

FIG. 1-2

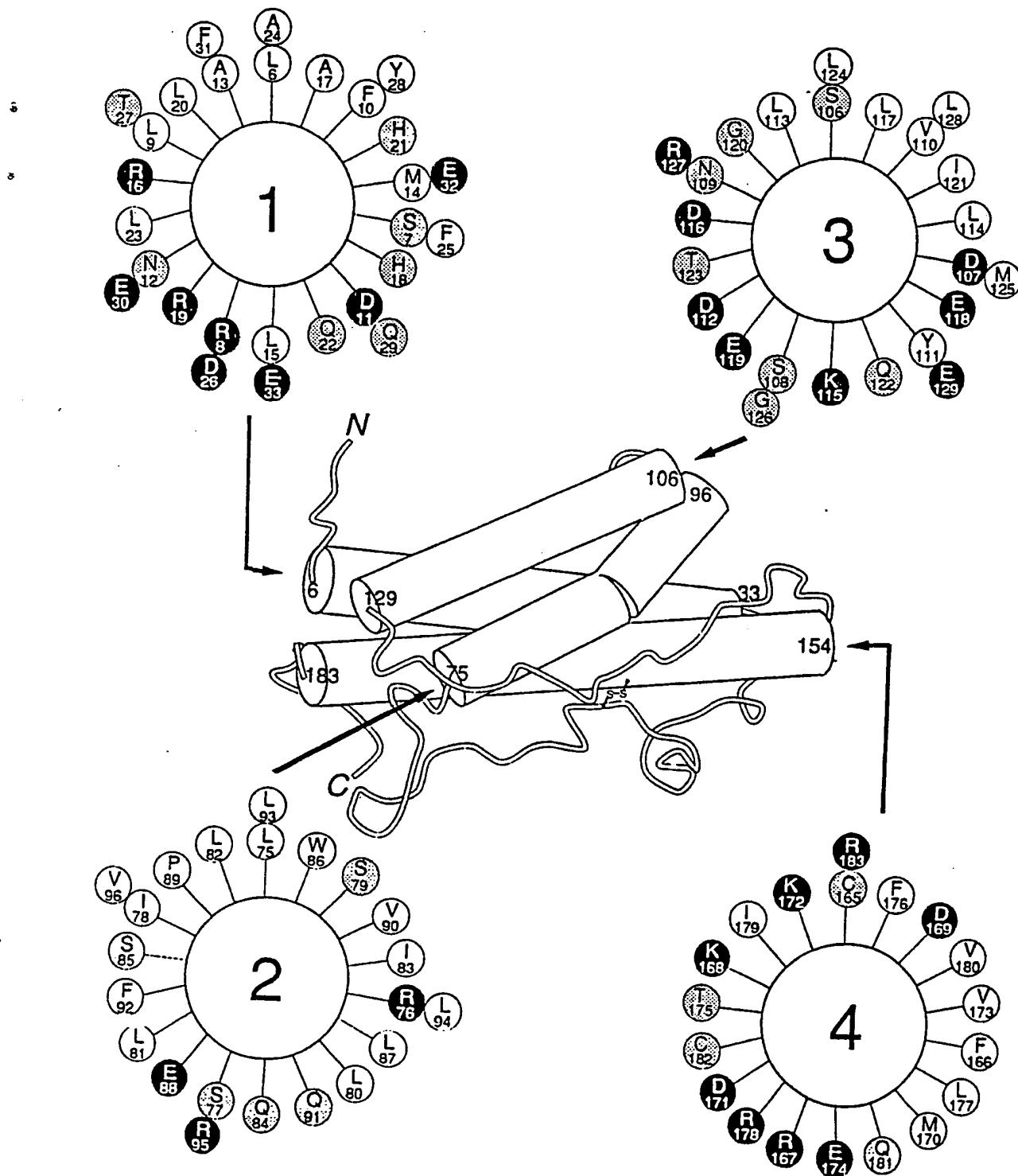


FIG.—3

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FIG.—4

Residue number in hGH

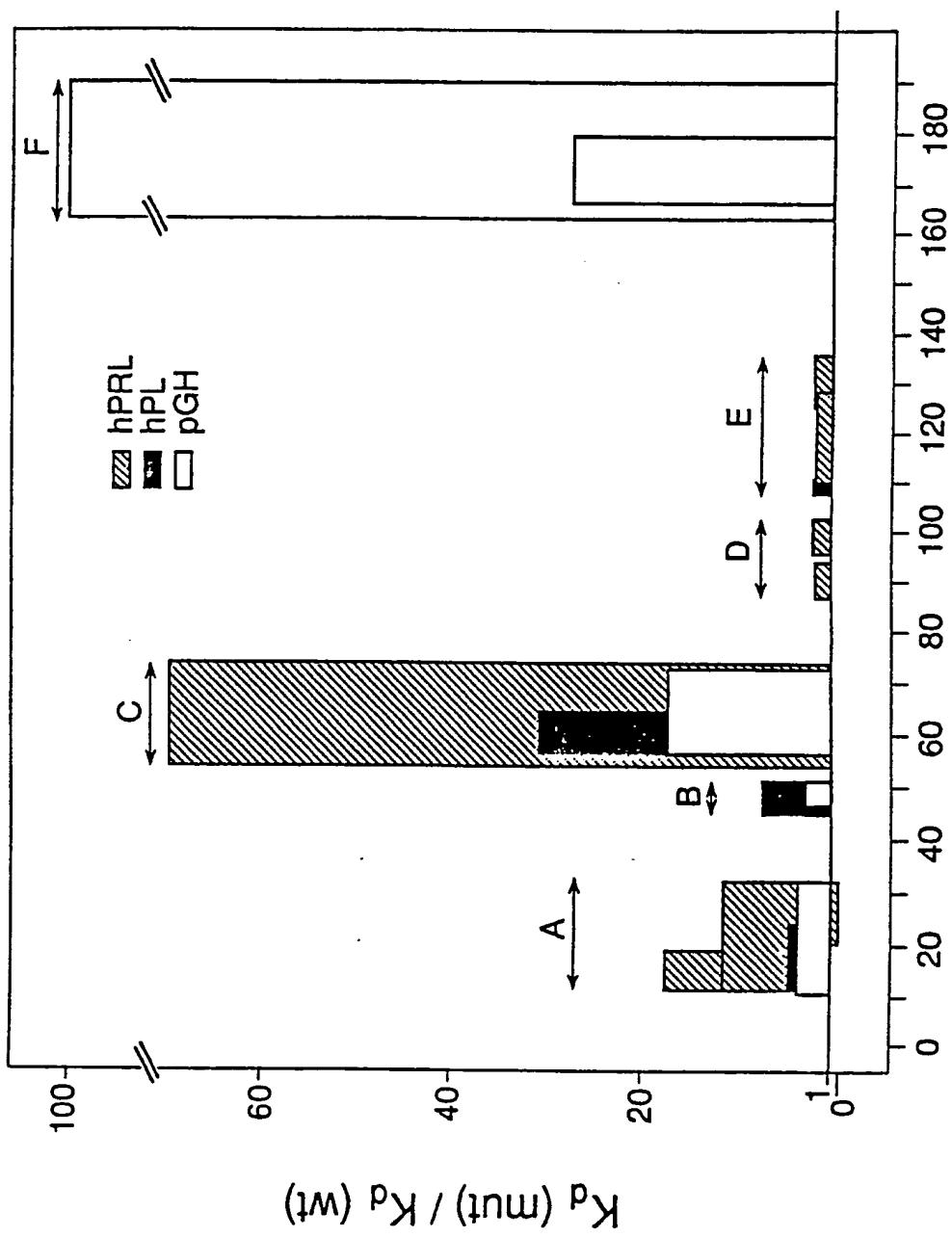
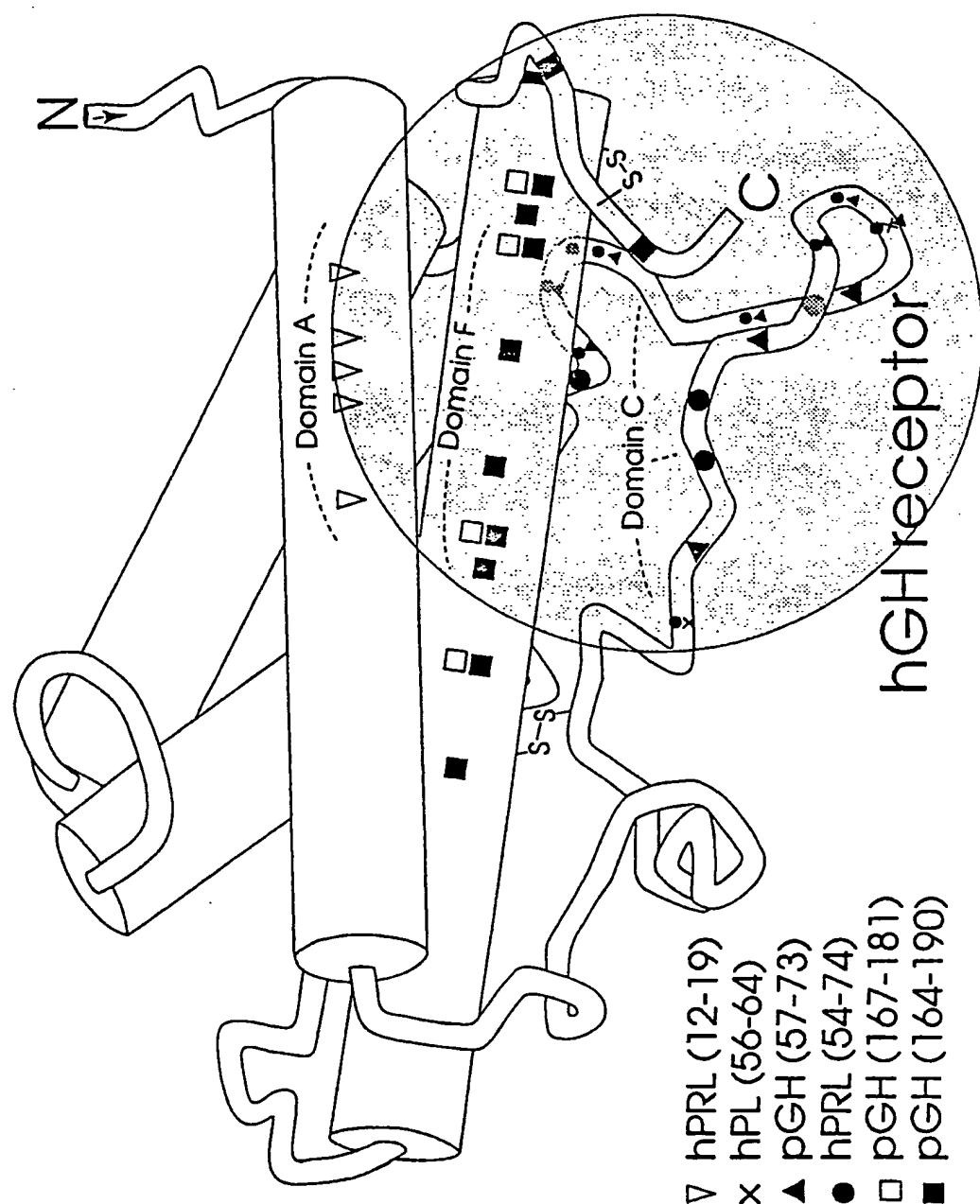


FIG.—5



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- hPRL (88-95)
- ▲ hPRL (97-104)
- hPL (109-112)
- ✗ hPRL (111-129) minus hPRL (126-136)

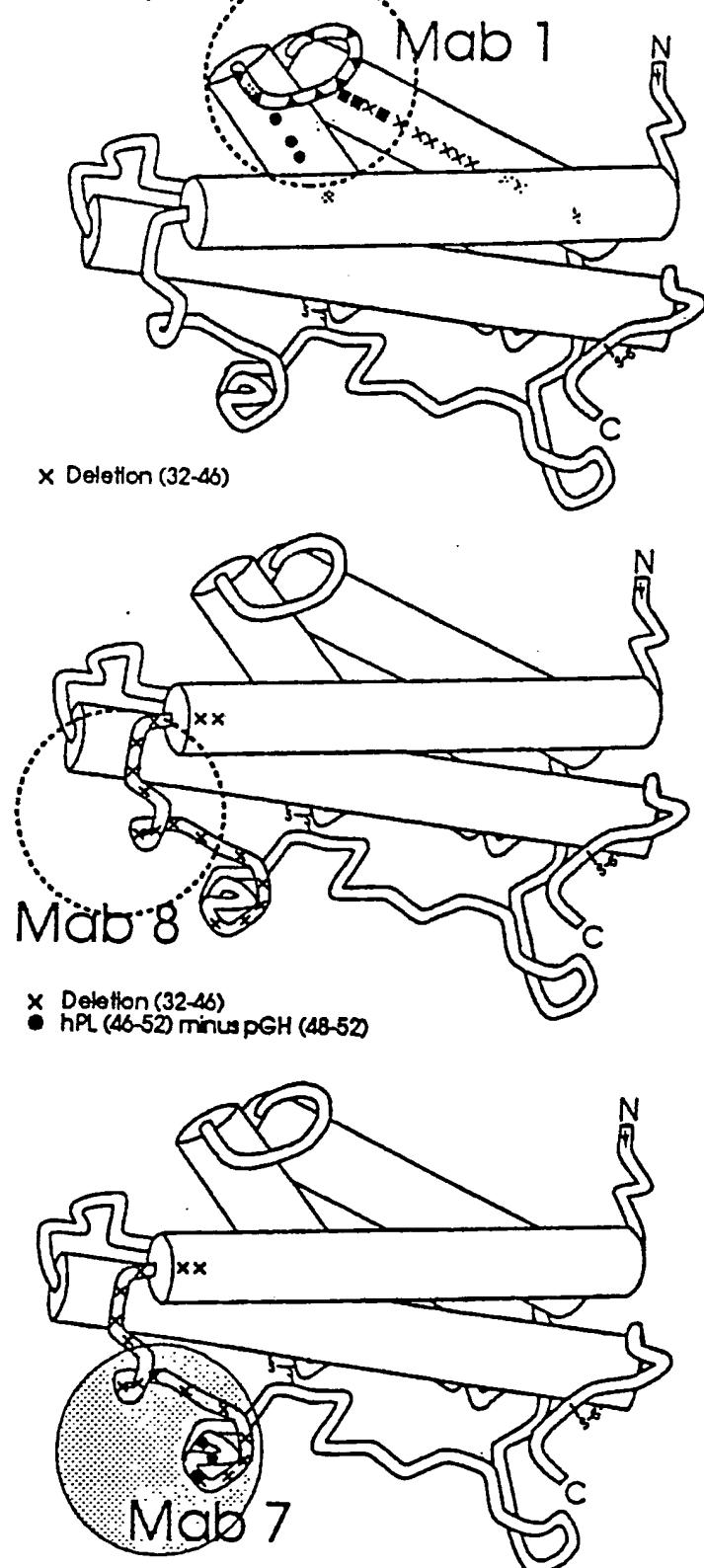
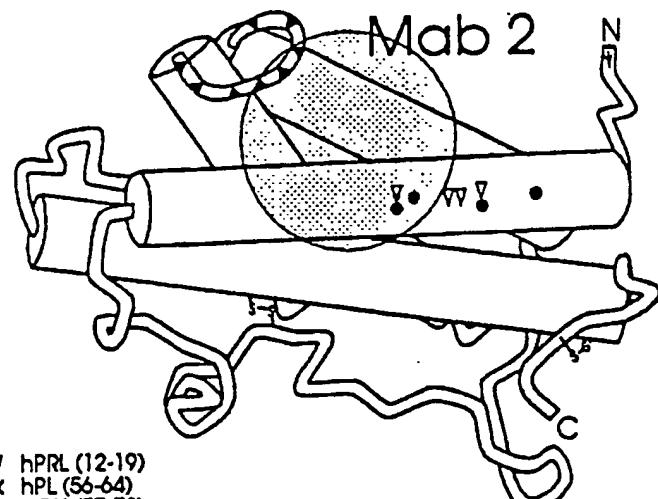


FIG.-6A

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- pGH (11-33) minus hPRL (22-33)
- ▽ hPRL (12-19) minus hPL (12-25)
- ▲ hPRL (97-104)



- ▽ hPRL (12-19)
- × hPL (56-64)
- ▲ pGH (57-73)
- hPRL (54-74)
- pGH (167-181)
- pGH (164-190)

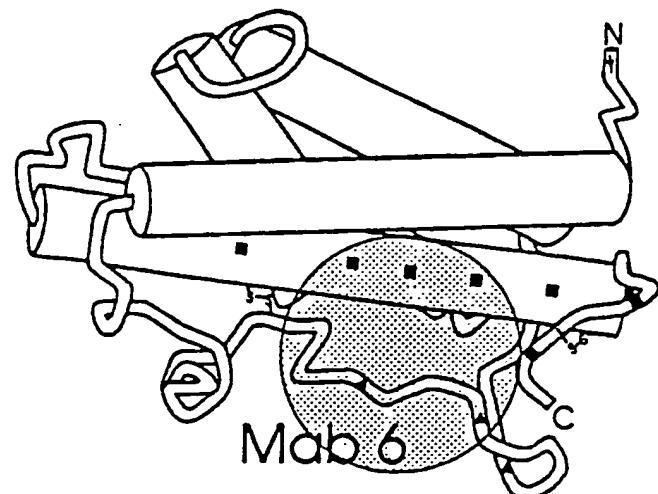
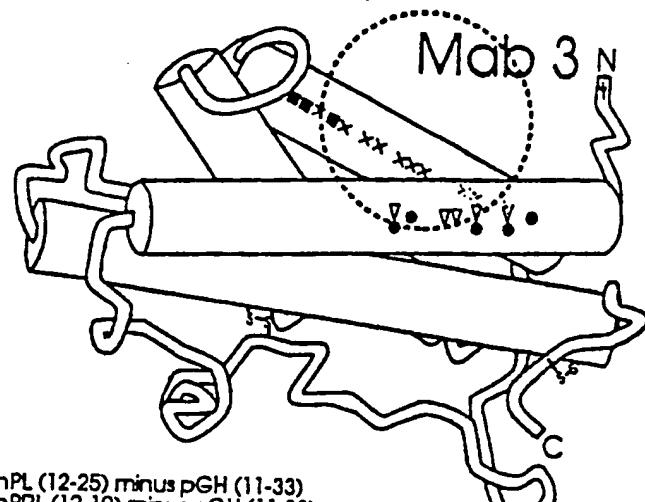


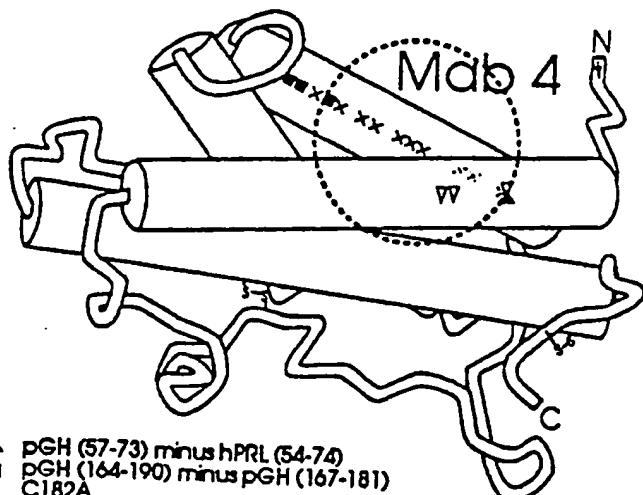
FIG.-6B

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- pGH (11-33) minus hPRL (22-33)
- ▲ hPL (12-25) minus hPRL (22-33)
- ▽ hPRL (12-79)
- hPL (109-112)
- × hPRL (111-129) minus hPRL (126-136)



- ▲ hPL (12-25) minus pGH (11-33)
- ▽ hPRL (12-19) minus pGH (11-33)
- hPL (109-112)
- × hPRL (111-129) minus hPRL (126-136)



- ▲ pGH (57-73) minus hPRL (54-70)
- pGH (164-190) minus pGH (167-181)
- C182A

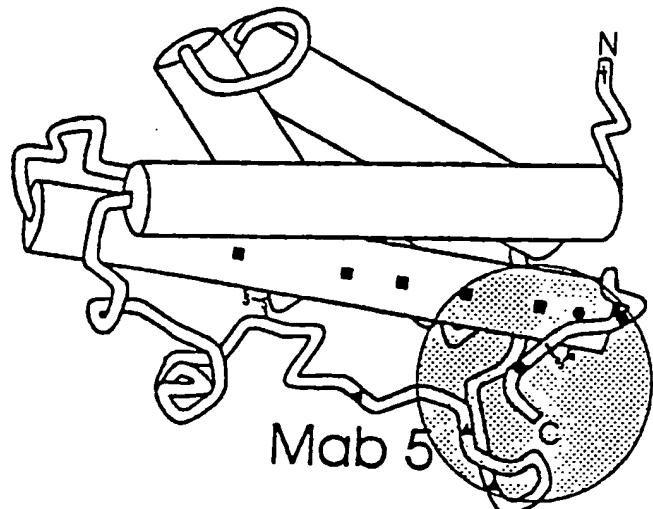
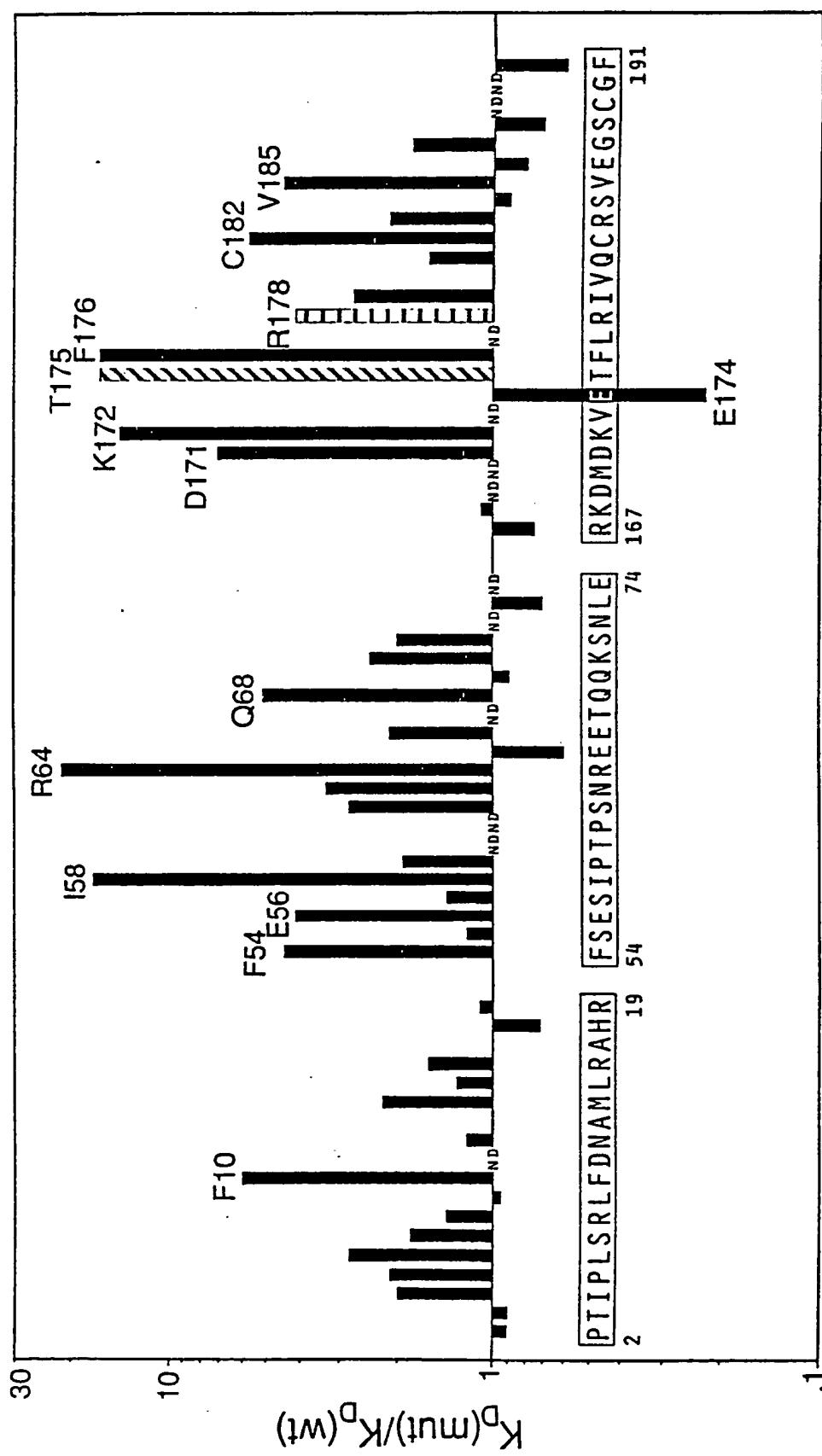


FIG.-6C

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Stronger binding → ← Weaker binding



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FIG.—7

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hGH Synthetic Gene

1 Met Lys Lys Asn Ile-Ala Phe Leu Leu Ala Ser Met Phe Val Phe Ser Ile Ala Thr Asn Ala Tyr Ala
 ATG AAA ARG ATC ATC GCA TTT CTT GCA TCT ATG TTC GTT TTT ATT GCT AAT GCC TAT GCA
NsiI

10 Phe Pro Thr Ile Pro Leu Ser Arg Leu Phe Asp Asn Ala Met Leu Arg Ala His Arg Leu His Gln Leu Ala
 79 TTC CCA ACT ATA CCA CTA AGT CGA CTA TTC GAT AAC GCT ATG CTT CGG GCC CAT CGT ATT CAG CTA GCC
Sall

20 Phe Asp Thr Tyr Gln Glu Glu Ala Tyr Ile Pro Lys Glu Gln Lys Tyr Ser Phe Leu Gln Asn Pro
 142 TTT GAC ACC TAC CAG GAG TTT GAA GAG GCG TAT ATC CCC AAG GAA CAG ATT TCA TTC CTG CAG AAC CCC
PstI

30 Gln Thr Ser Leu Cys Phe Ser Glu Ser Ile Pro Thr Pro Ser Asn Arg Glu Glu Gln Lys Ser Asn
 214 CAG ACC TCC CTC TGT TGC TCA GAA TCG ATT CCG ACA CCC TCC AAT CGC GAG CCC GTG CAG ATT TCC AAC
Clai

40 Leu Glu Leu Leu Arg Ile Ser Leu Leu Ile Gln Ser TRP Leu Glu Pro Val Gln Phe Leu Arg Ser Val
 286 CTA GAG CTC CTC CGC ATA AGC TGT CTG CTC ATC CAG TCG TCG TGT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
SacI

50 Leu Glu Leu Leu Arg Ile Ser Leu Leu Ile Gln Ser Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gln Lys Ser Asn
 358 TRC GCC AAC AGC CTC GTC TAC GGC TCT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
HindIII

60 Leu Glu Leu Leu Arg Ile Ser Leu Leu Ile Gln Ser Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gln Lys Ser Asn
 214 CAG ACC TCC CTC CGC ATA AGC TGT CTG CTC ATC CAG TCG TCG TGT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
NruI

70 Leu Glu Leu Leu Arg Ile Ser Leu Leu Ile Gln Ser Val Gln Phe Leu Arg Ser Val
 286 CTA GAG CTC CTC CGC ATA AGC TGT CTG CTC ATC CAG TCG TCG TGT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
XbaI

80 Phe Ala Asn Ser Leu Val Tyr GLY Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gln Lys Ser Asn
 358 TRC GCC AAC AGC CTC GTC TAC GGC TCT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
NarI

90 Leu Glu Leu Leu Arg Ile Ser Leu Leu Ile Gln Ser Val Gln Phe Leu Arg Ser Val
 214 CAG ACC TCC CTC CGC ATA AGC TGT CTG CTC ATC CAG TCG TCG TGT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
BamHI

100 Phe Ala Asn Ser Leu Val Tyr GLY Ala Ser Asp Ser Asn Val Tyr Asp Leu Leu Lys Asp Leu Glu Glu Gln Lys Ser Asn
 358 TRC GCC AAC AGC CTC GTC TAC GGC TCT GAT TCG AAC TCG TAC GAC CTG CAG AAC GAC CTA GAG GAA GGG
SacII

110 Ile Gln Thr Leu Met GLY Arg Leu Glu Asp GLY Ser Pro Arg Thr GLY Gln Ile Phe Lys Gln Thr Tyr Ser
 430 ATC CAA ACG CTC ATG GGG AGG CTG GAA GAT GGC AGC CCG CGG ACT GGG CAG ATC RTC AAC CAG ACC TAC AGC
BglII

120 Ile Gln Thr Leu Met GLY Arg Leu Glu Asp GLY Ser Pro Arg Thr GLY Gln Ile Phe Lys Gln Thr Tyr Ser
 358 TRC GCC AAC AGC CTC ATG GGG AGG CTG GAA GAT GGC AGC CCG CGG ACT GGG CAG ATC RTC AAC CAG ACC TAC AGC
BamHI

130 Ile Gln Thr Leu Met GLY Arg Leu Glu Asp GLY Ser Pro Arg Thr GLY Gln Ile Phe Lys Gln Thr Tyr Ser
 430 ATC CAA ACG CTC ATG GGG AGG CTG GAA GAT GGC AGC CCG CGG ACT GGG CAG ATC RTC AAC CAG ACC TAC AGC
SacII

140 Ile Gln Thr Leu Met GLY Arg Leu Glu Asp GLY Ser Pro Arg Thr GLY Gln Ile Phe Lys Gln Thr Tyr Ser
 358 TRC GCC AAC AGC CTC ATG GGG AGG CTG GAA GAT GGC AGC CCG CGG ACT GGG CAG ATC RTC AAC CAG ACC TAC AGC
BglII

150 Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr GLY Leu Leu Tyr Cys Phe Arg LYS
 502 AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC GCA CTA CTC AAC TAC AAC TAC GGC CTC TAC TGC TCT AGG AGG
MstI

160 Lys Phe Asp Thr Asn Ser His Asn Asp Asp Ala Leu Leu Lys Asn Tyr GLY Leu Leu Tyr Cys Phe Arg LYS
 574 AAG TTC GAC ACA AAC TCA CAC AAC GAT GAC GCA CTA CTC AAC TAC AAC TAC GGC CTC TAC TGC TCT AGG AGG
PvuII

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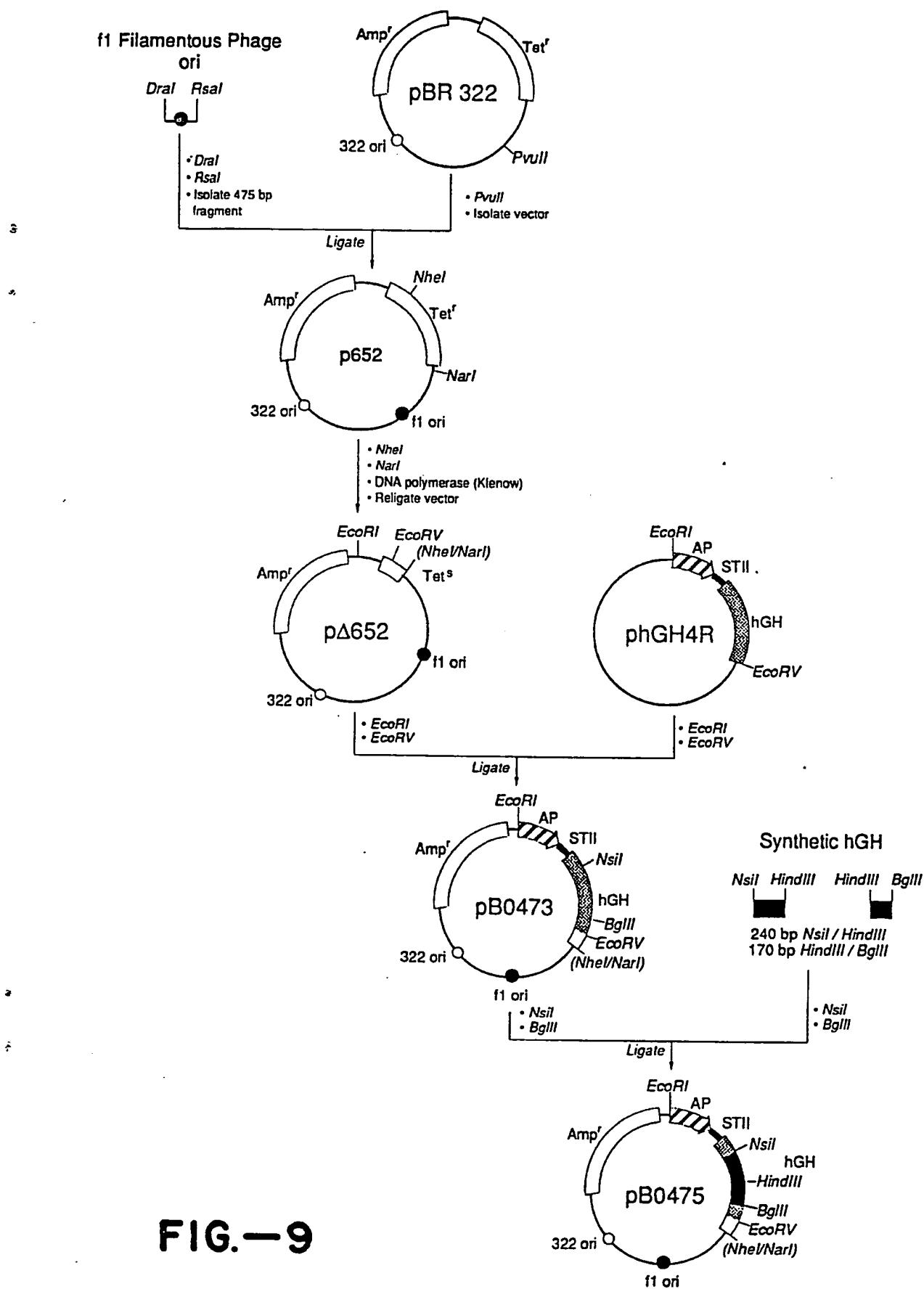


FIG.—9

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FIG.—IOE

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FIGURE 1

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FIGURE 10

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4241 CCGATCGTTC TCAGAAGTAA GTTGGCCGCA GTTGGTATCAC TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCTAT GCCATCCGTA AGATGCTTT
 GGCTAGCAAC AGCTCTATT CAAACGGGGT CACAATAGTG AGTACCAATA CGCTGGAC AGTAAAGG AATGACAGTA CGTAGGGCAT TCTACGAAAA
 ahari [M. hpari-] acyI msPI hpaII hpaII
 fnu4HI bbVI nlaIII foki sfaNI
 haerII eaeI cfrI nlaIII foki sfaNI
 dpnI Pvul CCGATCGTTC TCAGAAGTAA GTTGGCCGCA GTTGGTATCAC TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCTAT GCCATCCGTA AGATGCTTT
 GGCTAGCAAC AGCTCTATT CAAACGGGGT CACAATAGTG AGTACCAATA CGCTGGAC AGTAAAGG AATGACAGTA CGTAGGGCAT TCTACGAAAA
 ahari [M. hpari-] acyI msPI hpaII hpaII
 fnu4HI bbVI nlaIII foki sfaNI
 hphI rsaI scaI ddeI msPI hpaII hpaII
 bsrI CTCGACTCC TGAGTACTCA ACCAAACTCAT TCTGAGAATA GTGTTATGGGG CGACCGAGTT GTCTCTGGCC GGCGTCAACA CGGGATAATA CGCGCCACA
 GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTACATACGCC GCTGGCTCAA CGGAAACGGG CGCGAGTTGT GCCCTATTAT GGCGGGGTGT
 bsrI msPI hpaII hpaII
 fnu3AI mboI [dam-] msPI hpaII hpaII
 mboI [dam-] dpnI alwI
 msEI draI hgiAI bsp1286 xbaII mboII xbaII bsrI tagI
 4441 TAGCGAACT TAAAGTGC TCATCATTGG AAAACGTTCT TCGGGGGCAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT GTAAACCCACT
 ATCGTCTTCA AATTTCACG AGTAGTAAC TTTGCGAAGA AGCCCAGCTT TTGAGAGTTC CTAGAACTCA GACAATGGC GGTCAAGCTA CATGGGTGA
 mboII [dam-] msPI hphI
 hphI mboII [dam-] msPI hphI
 draI ahari bsp1286 xbaII mboII xbaII bsrI tagI
 4541 CGTGCACCA ACIGATCTTC AGCATCTTT ACTTCACCA GCCTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCG AAAAACCGA ATAAAGGGCA
 GCACGGGGT TGACTAGAAG TCCTAGAAA TGAAGTGGT CGCAAAAGAC CACTGGTTT TGCCCTTCG TTTTACGGG TTTCCTCCCT
 mboII msPI hphI
 earI ssPI bsmAI
 4641 CACGGAAATC TTGAAATACTC ATACTCTTC TTTTCAATA TATTTGAAGC ATTATCAGG GTTATTGCT CATGAGGGAA TACATATTTG AATGTTATTAA
 GTGCCCTTAC AACTATGAG TATGAGAAGG AAAAAGTTATAAATGTCG TAAATAGTCC CATAAACAGA GTACTGGCCT ATGTATAAAC TTACATAAAT

FIG.-101

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4741 GAAATATAA CAAATAGGGG ATTCCGGCAC ATTCCCCGA AAAGTGCAC CTGACGCTA AGAACCTT ATTATCATGA CATTAACTTA TAATAATAGG
 CTTTTATTG GTTATCCCCC AGGGGGCT TAAGGGGTAA TCTTACGGTG GACTGCAGAT TCTTTGGTAA TAATAGTACT GTAAATTGGAT ATTITTTATCC

sau96I [M. haemIII-]
 haemIII
 asuI
 eco0109I
 mnII
 CGTATACCGA
 GCATAGTGCT
 GGGCCCTTTCG
 TCTTCGA
 AGAACGT
 AGAACGT

:Length: 4867

aarI (GACGTC):
 accI (CTEKAC):
 accII (TCCGGA):
 acyI (GRCCYC):
 ahaiI (GRCCYC):
 ahaiII (TTTAAA):
 ahaiIII (TTTAAA):
 aluI (-GCT):
 alwI (GGATC):
 elwNI (CAGNNNTG):
 epaI (GGGCC):
 apalI (GTGCAC):
 aseI (ATTAAT):
 asuI (GGNCC):
 asuII (TTCGAA):
 avaI (CYCGRG):
 avaII (GGWCC):
 avaIII (ATGCAT):
 baliI (TGGCCA):
 bamHI (GGATCC):
 banI (GGYRC):
 banII (GRCCYC):
 bbvI (GCAGC):
 bclI [dam-] (TGATCA):
 hinPI
 hhaI
 fndII
 plalV bstUI [M. hhaI-]
 aatII
 acyI ddeII
 aatII
 bspHI
 mseI
 nlaIII
 ahaII
 acyI ddeII
 aatII
 bspHI
 mseI

4793
 4771 [M. taqI-] 761 2753
 1701 2108 2568
 767 4411 4793
 767 [M. hhaI-] 4411 [M. hpaII-] 4793
 3739 3758 450
 72 203 522 678 692 1019 1032 1040 2036 2093 2166 2423 2623 2642 2923 3149
 3239 3285 3542 4063 4163 4226
 816 817 1704 2105 2106 2571 2572 3549 3623 3635 3720 3733 4197 4500 4518
 728 3393
 504
 2798 3296 4542
 4046
 504 505 802 1182 1297 1476 1518 1797 1986 2328 3917 3996 4013 4235 4851
 778
 716 [M. taqI-] 1462
 802 1476 [dcm-] 1518 1797 4013 4235
 1481 [dcm-]
 816 2105 [M. mspl-] 2571 [M. mspl-]
 767 1086 1129 11326 2374 3823
 504 [M. haeII-] 677 [M. aluI-] 719 2408
 204 207 697 849 940 1017 1033 1236 1443 1467 1599 1722 2516 2621 2718 2887
 2905 3324 3389 3392 3598 3926 4115 4292

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bgII (GCCNNNNNGGC) : 3989 [M. haeiII-]
 bgII (AGATCT) : 867
 bsmI (GAATCC) : 182 455 1390
 bsmI (CTCTC) : 295 977 2631 3942 4707
 bspI (GCGCHC) : 504 [M. haeiII-] 677 [M. aluI-] 719 1502 2408 2798 3296 4457 4542
 bspI (TCATGA) : 3702 4710 4815
 bspI (CCCTGC) : 792
 bspI (TCCGGA) : 1701 2108 2568
 bspI (ACTGG) : 706 860 1220 1547 1818 1842 2250 2729 2757 3385 3398 3515 3921 4039 4082 4346
 bspI (TTCCGA) : 4521
 bspI (CCCGGG) : 778
 bspI (CCGGG) : 541 757 1140 1479 3009 3130 3143
 bspI (CCCTNAGG) : 211 [M. hhaI-] 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520 [M. hhaI-] 2540 [M. hhaI-]
 bspI (CCSGG) : 2564 [M. hhaI-] 2582 [M. hhaI-] 2584 [M. hhaI-] 2687 [M. hhaI-] 3028 3609 [M. hhaI-] 3939
 bspI (YGGCCR) : 4432 [M. hhaI-] 4764 [M. hhaI-]
 bspI (ATGGAT) : 750
 bspI (RGATCT) : 816 867 1704 2105 2571 3623 3634 3720 3732 4500 4517
 bspI (CCTNAGG) : 733
 bspI (CCCTNAGG) : 1180 1295 1521 1849 2627 26662 3361 4057 4408
 bspI (YGGCCR) : 290 1481 4263
 bspI (ATGGAT) : 625
 bspI (CTNAG) : 57 473 619 734 1618 1780 2792 3257 3666 3832 4372 4798
 bspI (GATC) : 139 817 868 1498 1705 2106 2572 3549 3624 3635 3643 3721 3733 3838 4179 4197
 bspI (TAAAT) : 4243 4501 4518 4554
 bspI (CACNNNGTC) : 3739 3758 4450
 bspI (CTTAAA) : 2332
 bspI (CCTNAGG) : 290 1481 4263
 bspI (YGGCCR) : 551 2860 4664
 bspI (CTCTTC) : 733
 bspI (CCTNAGG) : 793
 bspI (CTNNNNNAGG) : 801 1475 (dcm-) 1517 4850
 bspI (GAATTG) : 1
 bspI (CCGGG) : 541 757 1140 1479 3009 3130 3143
 bspI (GATATC) : 1195
 bspI (GCNGC) : 204 207 697 849 940 1002 1017 1033 1236 1245 1443 1446 1453 1467 1596 1599
 bspI (GGATG) : 1722 1803 2516 2538 2552 2621 2718 2771 2887 2905 2908 3026 3181 3324 3389 3392
 bspI (GGCG) : 3598 3926 4115 4265 4292 4387 4616
 bspI (GGATC) : 211 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520 2564 2582 2584
 bspI (GGATG) : 2687 3028 3609 3939 4432 4764
 bspI (TGCAG) : 238 703 1122 1143 1718 1807 1885 2046 2657 3855 4036 4323
 bspI (TGGCCA) : 987 1393 1491 4095
 bspI (WGGCCW) : 555 1481 2995 3006 3458
 bspI (RGCGCY) : 153 767 1242 1681 1764 2492 2856 3226
 bspI (GGCC) : 291 505 556 1183 1298 1482 1986 2186 2328 2996 3007 3025 3459 3917 3997 4264
 bspI (GGCC) : 4851

FIG.—10K

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hgar(GACGCC):
 hgiAI(GGCCWC):
 hgiCI(GGYRCC):
 hgiJI(GRGCYC):
 hhaI(GCCG):
 hhaPI(GCCG):
 hncII(GTYRAC):
 hndII(GTYRAC):
 hndIII(AGCCT):
 hneI(GATTC):
 hngII(CCGG):
 hphII(GGTGA):
 hphII(GAACG):
 hncI(dam-)(GATC):
 hnhII(CCTC):
 hnhII(CCCT):
 hneI(TTAA):
 hnpI(CCGG):
 hntI(TGCCGA):
 hnpII(CCCTNAGG):
 hael(GCCGGC):
 haRI(GCCGCC):
 hcII(CCSCG):
 hcdeI(CATATG):
 hheI(GCTGCC):
 hlaIII(CATG):
 hlaIV(GGNNCC):
 hnruI(TCGCGA):
 nsII(ATGCAT):
 nsPCIX(RCATGY):
 paeR7I(CTCGAG):
 pfIMI(CCANNNNNTGG):
 pheI(GATGC):
 ppuMI(RGGWCCY):
 pstI(CTGCAAG):
 917 1277 1427 2041 2565 2688 3084 3662 4412
 677 [M. aluI-] 1502 2798 3296 4457 4542
 767 1086 1129 1326 2374 3823
 504 677 719 2408
 112 154 210 768 988 1111 1243 1394 1456 1492 1682 1765 2485 2493 2519 2541 2550
 2563 2583 2686 2716 2857 2890 3160 3227 3327 3501 3610 4003 4096 4433 4765
 112 154 210 768 988 1111 1243 1394 1456 1492 1682 1765 2485 2493 2519 2541 2550
 2563 2583 2686 2716 2857 2890 3160 3227 3327 3501 3610 4003 4096 4433 4765
 477 [M. taqI-] 4414
 477 4414
 71 691
 623 [M. taqI-] 628 [M. taqI-] 776 [M. taqI-] 1341 [M. hphI-] 1562 [M. hphI-] 2068 2264
 2286 2882 2957 3353 3870
 1171 1180 1295 1321 1522 1702 1849 2109 2439 2569 2628 2662 3189 3336 3362 3552
 3956 4057 4167 4409
 380 1136 1344 1565 2346 2592 2601 3726 3953 4349 4575 4590
 409 514 551 744 842 870 [dam-] 1638 2465 2861 3632 [dam-] 3723 [dam-] 4478 4556 [dam-]
 4665 4861
 139 817 868 1498 1705 2106 2572 3549 3624 3635 3643 3721 3733 3838 4179 4197
 148 163 241 372 378 554 606 610 639 650 682 736 771 809 835 1013 1125 1185 1265
 1330 1330 1516 1830 1888 1944 2372 2579 2609 2871 3097 3154 3421 3821 3902 4032
 4238 4849
 69 257 324 1044 1066 1757 1979 2011 2125 2136 2148 2159 2176 2274 2545 2763
 3688 3740 3745 3759 3812 4047 4086 4451 4823
 1171 1180 1295 1321 1522 1702 1849 2109 [M. bamHI-] 2439 2569 [M. bamHI-] 2628 2662
 3189 3336 3362 3552 3956 3990 4057 4167 4409
 987 1393 1491 4095
 733
 1320 2438
 767
 1180 1295 1521 1849 2627 2662 3361 4057 4408
 2804
 523 [M. aluI-] 1239
 40 964 1288 1495 1629 1854 1918 1983 2618 2723 2983 3703 4194 4204 4282 4318
 4711 4816
 504 767 816 1086 1129 1291 1326 1361 1475 1518 1797 2105 2374 2395 2407 2571
 3012 3051 3823 3917 3958 4169 4759
 646
 453
 1853 2617 2982
 716
 14 1352 1401
 2264 2286 2882 3353 3870
 801 1475 1517
 590 4116 [M. H1-]

FIG.—IOL

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PvuI(CGATCG):
 PvuII(CAGCTG): 4242
 RsaI(GTAC): 270 1018[M.HI-]
 159 342 787 1174 2789 4354
 677
 SacI(GAGGTC): 677
 SalI(GTCCGAC): 854
 Sau3AI(GATC): 139 817 868 1498 1705 2106 2572 3549 3635 3643 3721 3733 3838 4179 4197
 477
 Sau96I(CGCC): 4243 4501 4518 4554
 SacI(M.haeIII-): 504[M.haeIII-] 505[M.haeIII-] 802 1182[M.haeIII-] 1297[M.haeIII-] 1476[dcm-]
 1518 1797 1986[M.haeIII-] 2328[M.haeIII-] 3917[M.haeIII-] 3996[M.haeIII-] 4013
 4235 4851[M.haeII-]
 4353
 SmaI(AGCTACT): 1180 1295 1521 1849 26627 2662 3361 4057 4408
 SacI(CCGGG): 541 557 1140 1479 3069 3130 3143
 SmaI(GCATC): 175 237 416 90 1144 1214 1458 1710 1719 1806 1884 1947 2658 2774 2829 2850
 3070 4122 4332 4562
 SmaBI(TACGTA): 217
 SpeI(ACTAGT): 338
 SpeI(ACCTTT): 2127 4677
 677
 SacI(GAGGTC): 555
 SmaI(AGCCCT): 567 1406
 SacI(CCWGG): 478 486 626[M.claI-] 717 779 894 975 1305 2370 3082 4526
 SacI(TCGA): 211 647 855 1271 1281 1426 1452 1574 1671 2043 2144 2520 2564 2582 2584
 SacI(CGCC): 2687 3028 3609 3939 4432 4764
 SphI(M(GACMNGTC): 968 2726
 XbaI(TCTAGA): 368
 XbaI(CTCGAG): 368
 XbaI(RGATCY): 716
 XbaI(CGGCCG): 816 867 1704 2105 2571 3623 3634 3720 3732 4500 4517
 XbaI(GAANNNNTIC): 290
 not found:
 KpnI(GCTTACCC), asp718(GGTACCC), avrII(CCTAGG), bssHII(GCGCGC), bstTEII(GGTNACC), espI(GCTNAGC), hpaII(GTTAAC), kpnI(GCTTACCC), ncoI(CCATTG), notI(GCGGCCGC), rsiI(CGGGCCG), sfiI(GGGGCCGC), smarI(CCCGGG), xbaI(GCATGC), xmaI(CCCGGG)

FIG.—10M

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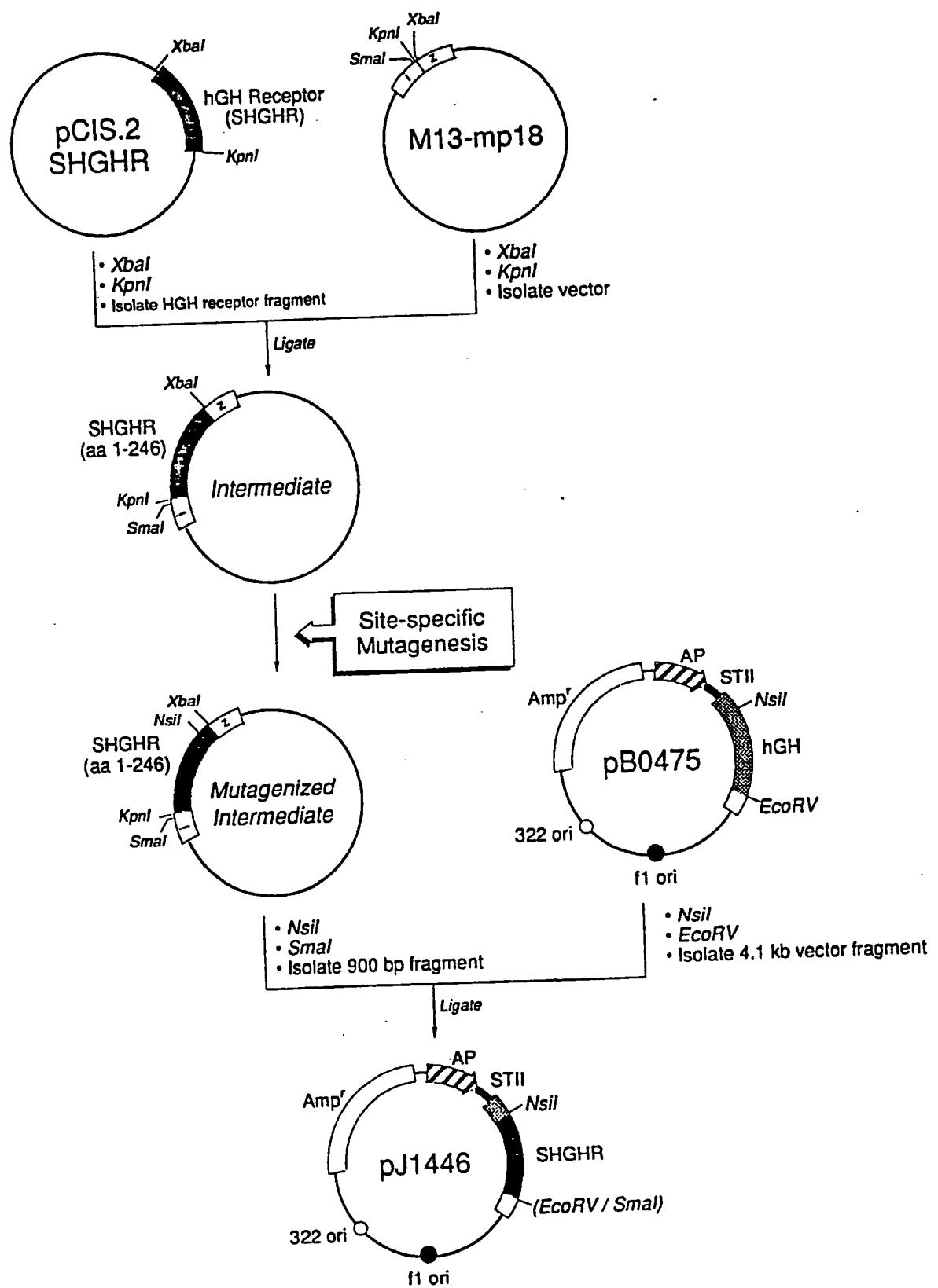


FIG.-II

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dralII hphI ddeI bsmAI nlaIII bsrI mnII nlaIII rsal stYI
 557 AAA TTC ACC AAG TGC CGT TCA CCT GAG CGA GAG ACT TTT TCA TGC CAC GAT GAG GAT GAT GGT ACA AAG AAC
 TTI AAG TGG TTC ACG GCA AGT GGA CTC GCT CTC TGA AAA AGT ACG GTG ACC TGT CTA CTC CAA GTA CCA TGT TTC TTG
 34 Lys Phe Thr Lys Cys Arg Ser Pro Glu Arg Glu Thr Phe Ser Cys His Trp Thr Asp Glu Val His His Gly Thr Lys Asn

sau96I nlaIV asuII
 nlaIV avaiI
 avaiI asuII
 ppMI aluI
 eco0109I pvuII pvuII bsrI hinfI mnII bsmI bsmI
 638 CTA CGA CCC ATA CAG CTG TTC TAT ACC AGA AGC AAC ACT CAA GAA TGG ACT CAA GAA TGG AAA GAA TGC CCT GAT TAT GTT
 GAT CCT GGG TAT GTC GAC AAG ATA TGG TCT TCC TGT TGA GTT CTT ACC TGT CTA CTC GGA CTA ATA CAA
 61 Leu Gly Pro Ile Glu Leu Phe Tyr Thr Arg Arg Asn Thr Glu Trp Thr Glu Trp Lys Glu Trp Lys Glu Cys Pro Asp Tyr Val

pleI aluI
 719 TCT GCT GGG GAA AAC AGC TGT TAC TTT AAT TCA TCG TTT ACC TCC ATC TGG ATA CCT TAT TGT ATC AAG CTA ACT AGC AAT
 AGC CGA CCC CTT TTG TCG ACA ATG AAA TTA AGT AGC AAA TGG AGG TAG ACC TAT GGA ATA ACA TAG TTC GAT TGA TCG TTA
 88 Ser Ala Gly Glu Asn Ser Cys Tyr Phe Asn Ser Ser Phe Thr Ser Ile Trp Ile Pro Tyr Cys Ile Lys Leu Thr Ser Asn
 these first 9 bases differ from 262 and 265

sau3AI aluI
 mboI [dam-]
 dpmI
 alwI
 xhoII bsrI mnII bsrI mnII bsrI
 800 GGT GGT ACA GTG GAT GAA AAG TGT TTC TCT GAT GAA ATA GTG CAA CCA GAT CCA CCC ATT GGC CTC AAC TGG ACT TTA
 CCA CCA TGT CAC CTA CTT TTC ACA AAG AGA CAA CTA CTT TAT CAC GGT CTA GGG TAA CGG GAG TTG ACC TGA AAT
 115 Gly Thr Val Asp Glu Lys Cys Phe Ser Val Asp Glu Ile Val Gln Pro Pro Ile Ala Leu Asn Trp Thr Leu

bsrI hinfI nlaIII ecovI fokI mnII
 881 CTG AAC GTC AGT TTA ACT GGG ATT CAT GCA GAT ATC CAA GTG AGA TGG GAA GCA CCA CGC ATT GCA GAT ATT CAG AAA GGA
 GAC TTG CAG TCA ATT TGA CCC TAA GCA CGT CTA TAG GTT CAC TCT ACC CTT CGT GGT GCG TAA CGT CTA TAA GTC ATT CCT
 142 Leu Asn Val Ser Leu Thr Gly Ile His Ala Asp Ile Gln Val Arg Trp Glu Ala Pro Arg Asn Ala Asp Ile Gln Thr Leu

sau96I fokI mnII
 962 TGG ATG GTT CTG GAG TAT GAA CTT CAA TAC AAA GAA GTA ATT GAA ACT AAA TGG AAA ATG ATG GAC CCT ATA TTG ACA
 ACC TAC CAA GAC CTC ATA CTT GAA GTF ATT CTT CAT TTA CTT TGA ATT ACC TTT TAC TAC CTG GGA TAT AAC TGT TGT
 169 Trp Met Val Leu Glu Tyr Glu Leu Gln Tyr Glu Val Asn Glu Thr Lys Trp Lys Met Net Asp Pro Ile Leu -hr Thr

FIG.-12B

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FIG. 12C

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FIG.—12D

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FIG. 1

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FIG. 2G

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1601	AAAAGTGCTC ATCATGGAA AACGTTCTC GGGCGAAA CTCTCAAGGA TCTTACCGCT GTTGAGATCC AGTTCGATGT AACCCACTCG TGCACCCAAC	bsp1286	bsp1286	bsrI	sau3AI	sau3AI	sau3AI
	TTTCACGAG TAGAACCTT TTGCAAGAAG CCCGCTTT GAGAGTTCT AGAATGGCGA CAACTCTAGG TCAAGCTACA TTGGGTGAGC ACGTGGTTG	mboII	mboII [dam-]	mbol	mboI [dam-]	dpnI	dpnI
	mboII [dam-]	sau3AI	mboI [dam-]	dpnI	dpnI	dhAI	dhAI
1701	TGATCTCAG CATCTTAC TTTCACGAG GTTCTGGT GAGCAAAAC AGGAAGCCAA ATGGCCGAA AAAAGGAAT AAGGGCAGCA CGGAATGTT	dpnI	dpnI	dhAI	dhAI	bspI	bspI
	ACTAGAAGTC GTAGAAATG AAAGTGGTCC CAAAGACCCA	sfanI	sfanI	bspI	bspI	bspI	bspI
		hphI	hphI	bspI	bspI	bspI	bspI
4801	GAATACTCAT ACTCTTCCTT TTTCATATT ATTGAAGCAT TTATCAGGGT TATTGTCTCA TGAGGGATA CATATTTGAA TGTATTTGAA AAAATAACA	mbol	earI	sspI	bsmaI	bsmaI	bsmaI
	CTTATGGTA TGAAGGAA AAAGTATAA TAATCTCGTA AATAGTCCCA ATAACAGAGT ACTCGCCAT GTATAAATCT GTATTTATGTT	mboII	earI	sspI	bsmaI	bsmaI	bsmaI
		hinPI	hinPI	hinPI	hinPI	hinPI	hinPI
		haiI	haiI	haiI	haiI	haiI	haiI
		frudII	frudII	frudII	frudII	frudII	frudII
4901	ATAAGGGTT CGCGCACAT TTCCCCAAA AGTGCACCT GACGTCTAAG AAACCATTAAT TATCATGACA TAAACTATA AAAATAGGGC TATCACGAGG	nlaiI	nlaiI	nlaiI	nlaiI	nlaiI	nlaiI
	TTATCCCCAA GGCGGTGTA AAGGGCTTT TCACGGTTGA	mboII	mboII	mboII	mboII	mboII	mboII
5001	CCCTTTCGTC TTCAA	4941	4941	4941	4941	4941	4941
	GGGAAAGCAG AGCTT	2901	2901	2901	2901	2901	2901
		aaII (GACGTC):					
		accI (GTNKAC):					
		accII (TCCGGA):					
		acyI (GRCGTC):					
		ahAI (GRCGTC):					
		ahaiII (TTAA):					
		ahaiI (AGCT):					
		length: 5015					
		aaII (GACGTC):					
		accI (GTNKAC):					
		accII (TCCGGA):					
		acyI (GRCGTC):					
		ahAI (GRCGTC):					
		ahaiII (TTAA):					
		ahaiI (AGCT):					
		4941	4941	4941	4941	4941	4941
		2901	2901	2901	2901	2901	2901
		1849	2256	2716	4559	4941	4941
		4559	4941	4941	4559	4941	4941
		3887	3906	4598	3887	3906	4598
		72	203	271	481	651	734
		3433	3690	4211	4311	4374	4374
		3690	4211	4311	4374	4374	4374
		2184	2241	2314	2571	2790	3071
		1223	2241	2314	2571	2790	3071
		3387	3387	3387	3387	3387	3387

FIG.—12J

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aiwi(GGATC):	851 1095 1339 1340 1852 2253 2254 2719 2720 3697 3771 3783 3868 3881 4345 4648
aiwi(CGGNNCTG):	4666
aiwi(GTCAC):	3541
asei(ATTAAT):	2946 3444 4690
asei(ATTAAT):	4194
asui(GGNC):	641 1024 1445 1624 1666 1945 2134 2476 4065 4144 4161 4383 4999
asai(CYGRG):	1610
asai(GGZCC):	641 1024 1624 [dcm-] 1666 1945 4161 4383
asai(ATGCAT):	453
asrii(CCTAGG):	637
bali(TGCCCA):	1629 [dcm-]
bamHI(GGATCC):	1339 2253 [M.mspI-] 2719 [M.mspI-]
hani(GGYRCC):	1474 2522 3971
bani(GRCYC):	2556
hvi(GCAGC):	204 207 479 1221 1384 1591 1615 1744 1747 1870 2664 2769 2866 3035 3053 3472
bcII(dam-)(TGATCA):	138
bgII(GCCNNNNNGGC):	4137 [M.haeIII-]
bsmI(GAATGC):	182 701 1289 1538
bsmI(GTCTC):	295 587 2779 4090 4855
bspI286(GDGHC):	495 1139 1650 2556 2946 3444 4605 4690
bsphi(TCATGA):	3850 4858 4963
bspwi(TCCGGA):	1849 2256 2716
bsri(ACTGG):	603 870 896 1049 1368 1695 1966 1990 2398 2877 2905 3533 3546 3663 4069 4187
bsvII(CCWGG):	4230 4494 4669
bstII(CGGC):	501 524 1627 3157 3278 3291
bstII(CGGC):	211 [M.hhaI-] 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668 [M.hhaI-] 2688 [M.hhaI-]
bstII(CGGC):	2712 [M.hhaI-] 2730 [M.hhaI-] 2732 [M.hhaI-] 2835 [M.hhaI-] 3176 3757 [M.hhaI-] 4087
bstXI(RGATCY):	4580 [M.hhaI-] 4912 [M.hhaI-]
bstXI(RGATCY):	850 1094 1339 1852 2253 2719 3771 3782 3868 3880 4648 4665
cavII(CCSGG):	1443 1669 1997 2775 2810 3509 4205 4556
cfrI(YGGCCR):	290 1199 1629 4411
cdeI(CTNAGG):	57 488 546 579 1158 1766 1928 2940 3405 3814 3980 4520 4946
clpII(GATC):	139 851 1095 1340 1646 1853 2254 2720 3697 3772 3783 3791 3869 3881 3986 4327
dral(TTTAAA):	4345 4391 4649 4666 4702
dral(CACNNNGTG):	3887 3906 4598
eaei(YGGCGR):	562 2480
eaei(YGGCGR):	290 1199 1629 4411
eaig(CGGCCG):	290 1199
earI(CTCCTC):	3008 4812
eco0109I(RGGNCCY):	640 1623 [dcm-] 1665 4998
ecori(GAATT):	1
ecori(CCWGG):	501 524 1627 3157 3278 3291
ecori(GATTC):	911

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fncII(H(GCNGC)) : 204 207 479 1198 1201 1221 1384 1393 1472 1591 1594 1601 1615 1744 1747 1870
 1951 2664 2686 2700 2769 2866 2919 3035 3053 3056 3174 3329 3472 3537 3540 3746
 4074 4263 4413 4440 4535 4764
 211 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668 2712 2730 2732 2835
 fokI(TGATG) : 3176 3757 4087 4580 4912
 fspI(TGGCCA) : 238 811 959 963 1866 1955 2033 2194 2805 4003 4184 4471
 haei(WGGCCW) : 1541 1639 4243
 haei(TGGCCY) : 153 1390 1829 1912 2632 2640 3004 3374
 haclII(GGCC) : 291 472 527 1200 1446 1630 2134 2334 2476 3144 3155 3173 3607 4065 4145 4412
 4999
 hqai(GACCC) : 1425 1575 2189 2713 2836 3232 3810 4560
 hgai(GWGCMC) : 495 1139 1650 2946 3444 4605 4690
 hgicI(GYRCC) : 1474 2522 3971
 hqjII(GRGCYC) : 2556
 hhai(GGCC) : 112 154 210 1391 1542 1604 1640 1830 1913 2633 2641 2667 2689 2698 2711 2731
 2834 2864 3005 3038 3308 3375 3475 3649 3758 4151 4244 4581 4913
 hinpI(GCCG) : 112 154 210 1391 1542 1604 1640 1830 1913 2633 2641 2667 2689 2698 2711 2731
 2834 2864 3005 3038 3308 3375 3475 3649 3758 4151 4244 4581 4913
 hinclI(GTYRAC) : 1206 4562
 hindII(GTYRAC) : 1206 4562
 hindII(AGCTT) : 71
 hinfi(GAATC) : 505 685 901 1489 [M.hphII-] 1710 [M.hphII-] 2216 2412 2434 3030 3105 3501 4018
 hpaI(GTAAAC) : 1206
 hpaII(GCGG) : 1443 1469 1670 1850 1997 2257 2587 2717 2776 2810 3337 3484 3510 3700 4104 4138
 4205 4315 4557
 380 561 575 1492 1713 2494 2740 2749 3874 4101 4497 4723 4738
 409 542 1181 1184 1786 2613 3009 3780 [dam-] 3871 [dam-] 4626 4704 [dam-] 4813
 5009
 mboI [dam-] (GATC) : 139 851 1095 1340 1646 1853 2254 2720 3697 3772 3783 3791 3869 3881 3986 4327
 4345 4391 4649 4666 4702
 148 163 241 372 378 470 614 759 865 1136 1157 1413 1451 1478 1664 1978 2036
 2092 2520 2727 2757 3019 3245 3302 3569 3969 4050 4180 4386 4997
 69 257 324 519 744 893 1207 1905 2127 2159 2273 2284 2296 2307 2324 2422 2693
 2911 3836 3888 3893 3907 3960 4195 4234 4599 4971
 mspI(CCGG) : 1443 1469 1670 1850 1997 2257 [M.bamHI-] 2587 2717 [M.bamHI-] 2776 2810 3337 3484
 3510 3700 4104 4138 4205 4315 4557
 mstI(TGGCA) : 1541 1639 4243
 naei(GCCGGC) : 1468 2586
 ncII(CCGGG) : 1443 1669 1997 2775 2810 3509 4205 4556
 ndei(CATATG) : 2952
 nhei(GCTAGC) : 1387

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nlaIII(CATG) : 40 597 623 905 1176 1332 1436 1643 1777 2002 2066 2131 2766 2871 3131 3851 4342
 4352 4430 4466 4859 4964
 550 641 1024 1339 1439 1474 1509 1623 1666 1945 2253 2522 2543 2555 2719 3160
 319 3971 4065 4106 4317 4907
 119 8
 nol(GGGCCGC) :
 nsi(ATGGCAT) : 453
 nspCIx(RCATGY) : 1175 2001 2765 3130
 pflmI(CCANNNNNTGG) : 14 1500 1549
 pslI(GAGTC) : 505 685 2412 2434 3030 3501 4018
 ppumI(RGGWCCY) : 640 1623 1665
 pvtI(CGCGAG) : 4264 [M.H1-]
 pvtI(CGATCG) : 4390
 psalI(GTAC) : 270 650 733
 psalI(GTAC) : 159 342 627 804 1054 2937 4502
 psu3RI(GATC) : 139 851 1095 1340 1646 1853 2254 2720 3697 3772 3791 3869 3881 3986 4327
 4345 4391 4649 4666 4702
 sru96I(GGNCC) : 641 1024 1445 [M.haeIII-] 1624 [dcm-] 1666 1945 2134 [M.haeIII-] 2476 [M.haeIII-]
 4065 [M.haeIII-] 4144 [M.haeIII-] 4161 4383 4999 [M.haeIII-]
 scbI(AGTACT) : 4501
 scrFI(CCSSG) : 1443 1669 1997 2775 2810 3509 4205 4556
 scrFI(dcm-)(CCWGG) : 501 524 1627 3157 3278 3291
 sfAKI(GCATC) : 175 237 416 1252 1362 1606 1858 1867 1954 2032 2095 2806 2922 2977 2998 3218
 427 0 4480 4710
 217
 shabI(TACGTA) : 217
 sreI(ACTAGT) : 338
 ssPI(AATT) : 2275 4825
 stuI(AGGCCT) : 526 [dcm-]
 stvI(CCWMGG) : 637 1554
 taqI(TCGA) : 1453 2518 3230 4674
 thaI(CGCG) : 211 1203 1419 1429 1574 1600 1722 1819 2191 2292 2668 2688 2712 2730 2732 2835
 3176 3757 4087 4580 4912
 rhl1II(GACNNNGTC) : 2874
 xbaI(TCTAGA) : 368
 xhoI(RGATCY) : 850 1094 1339 1852 2253 2719 3771 3782 3868 3880 4648 4665
 xmaII(CGGCCG) : 290 1199
 xmnI(GAAANNNTTC) : 2216 4618
 not found:

afII(CTTAAG), apAI(GGGCCC), asp71B(GGTAC), asuII(TTCGAA), bglII(AGATCT), bspMI(ACCTGC), bssHII(GCGCCG),
 bstBI(TTCGAA), bstXI(GGNNACC), bsu36I(CCTNAGG), clAI(ATCGAT), ecc81I(CCTNNNNNAGG),
 espI(GCTNAGC), kpnII(GCTACC), mluI(ACCCGT), mstII(CCTNAGG), nraI(GGCAGC), nruI(TCGGA),
 rsrII(CGGWCCG), sacII(GAGCTC), salI(CCAGGG), smal(CTCGAC), sfiI(GTCGAC), smal(CCAGGG),
 sstII(GAGCTC), xbaI(TCTGAG), xmaI(CCCGGG)

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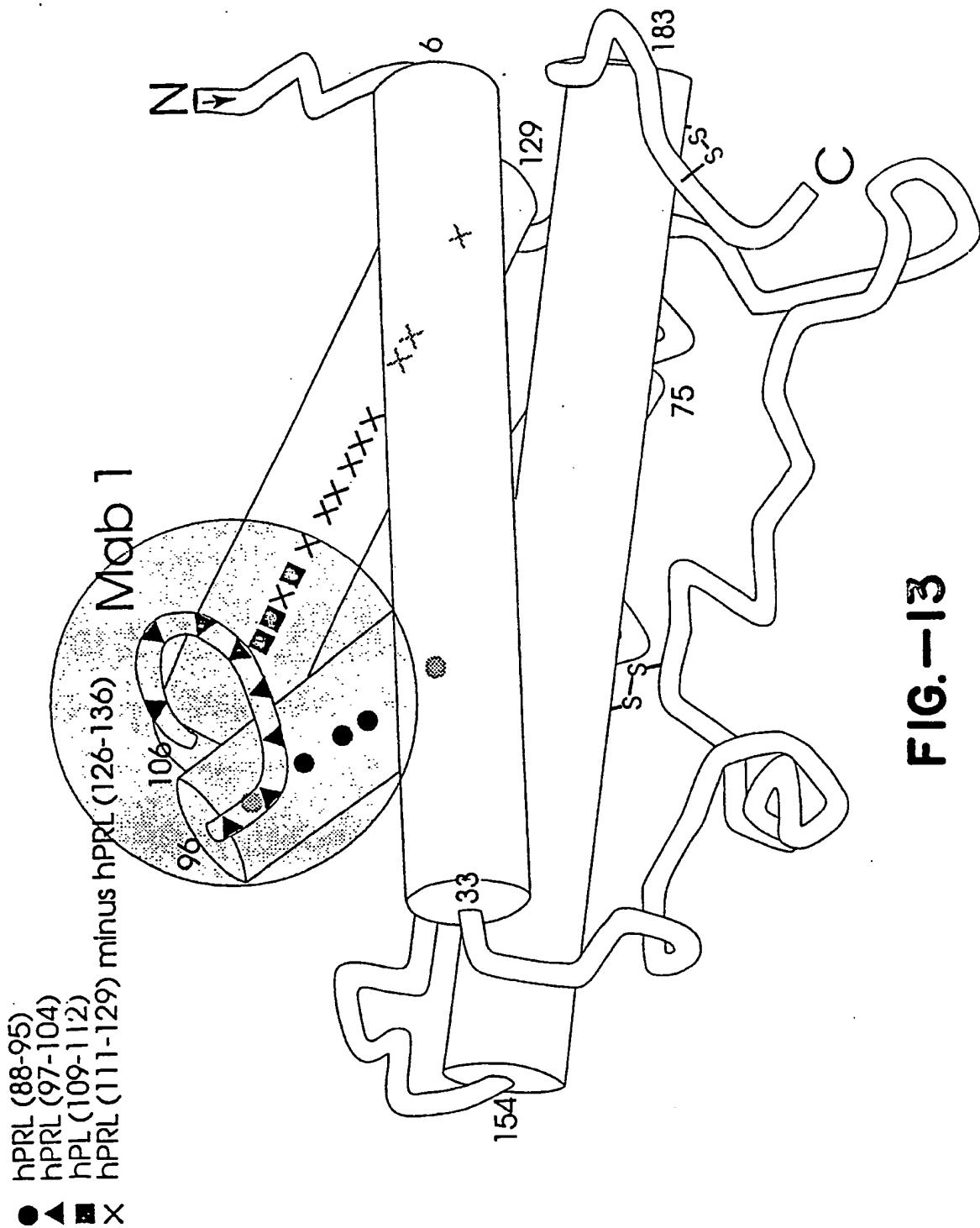
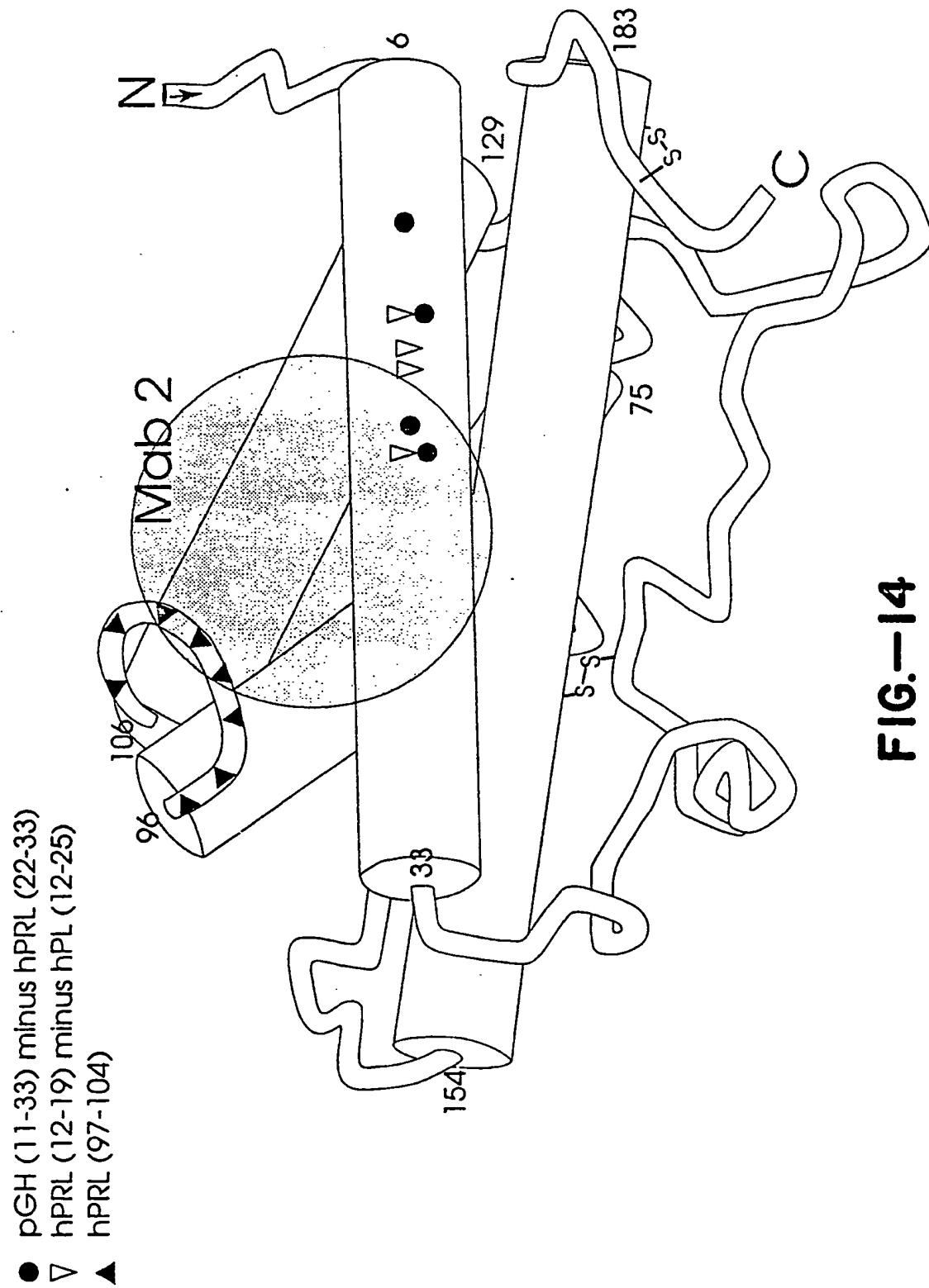


FIG.-13

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**FIG.—14**

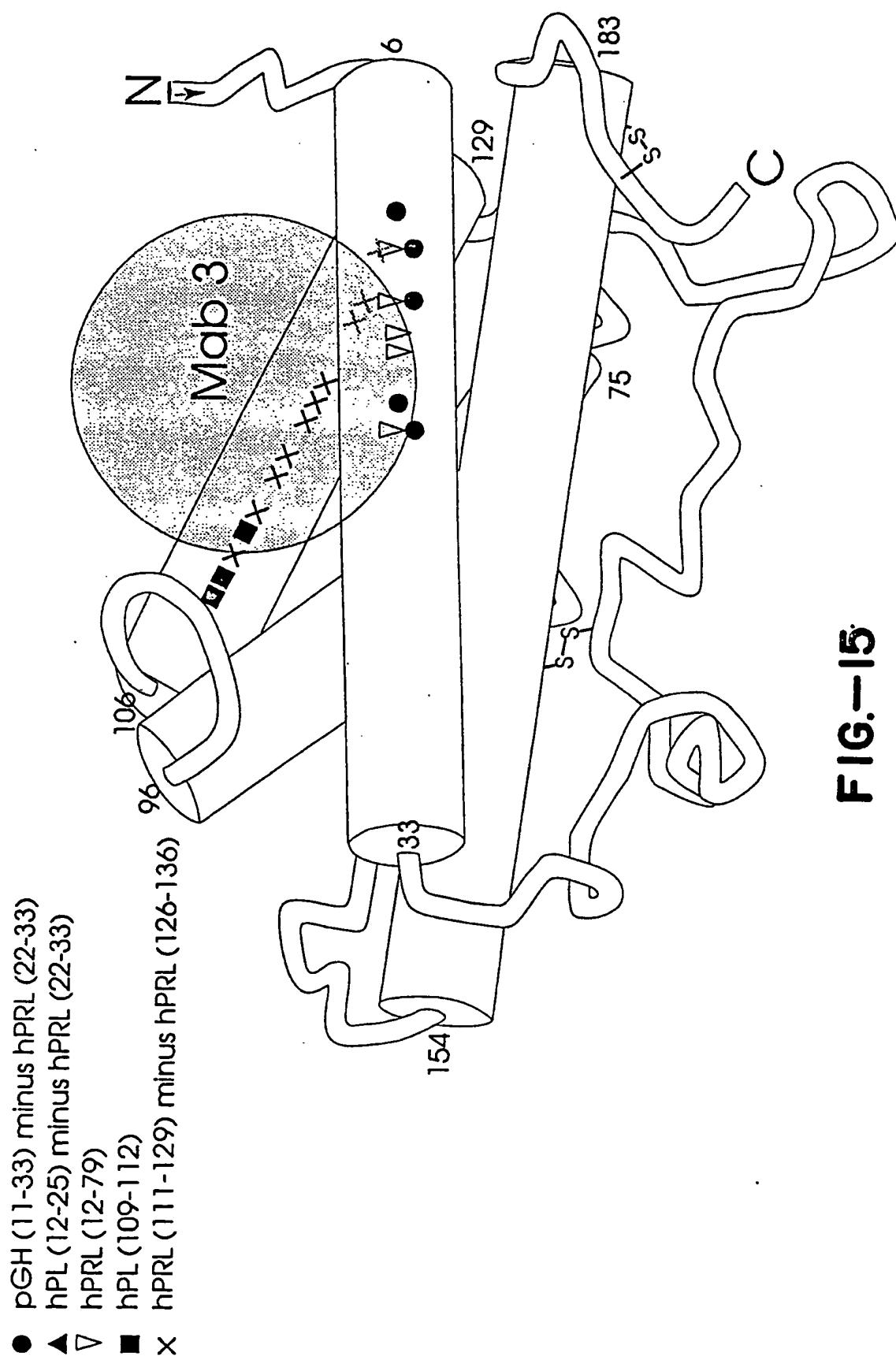


FIG.—15

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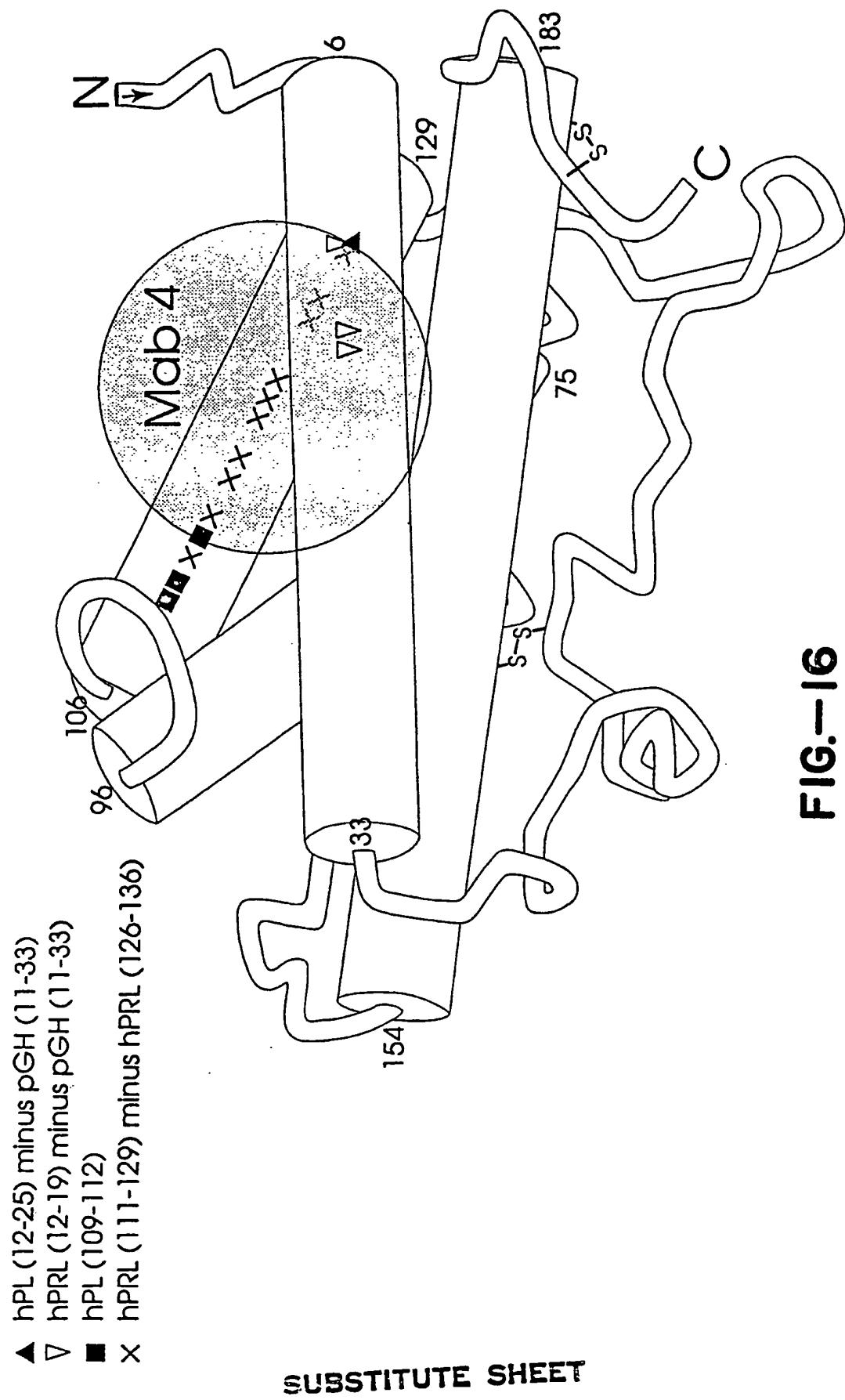
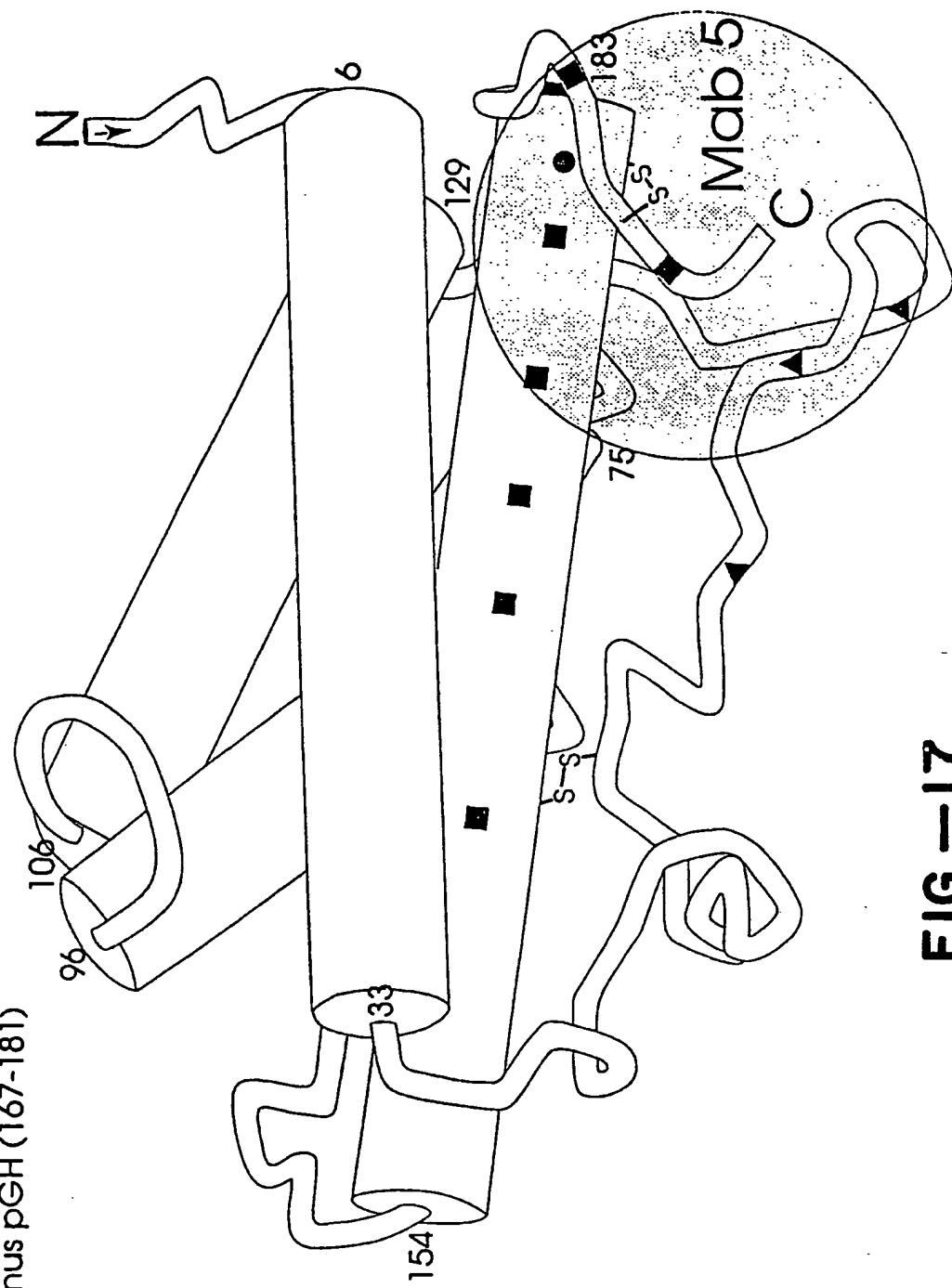


FIG.-16

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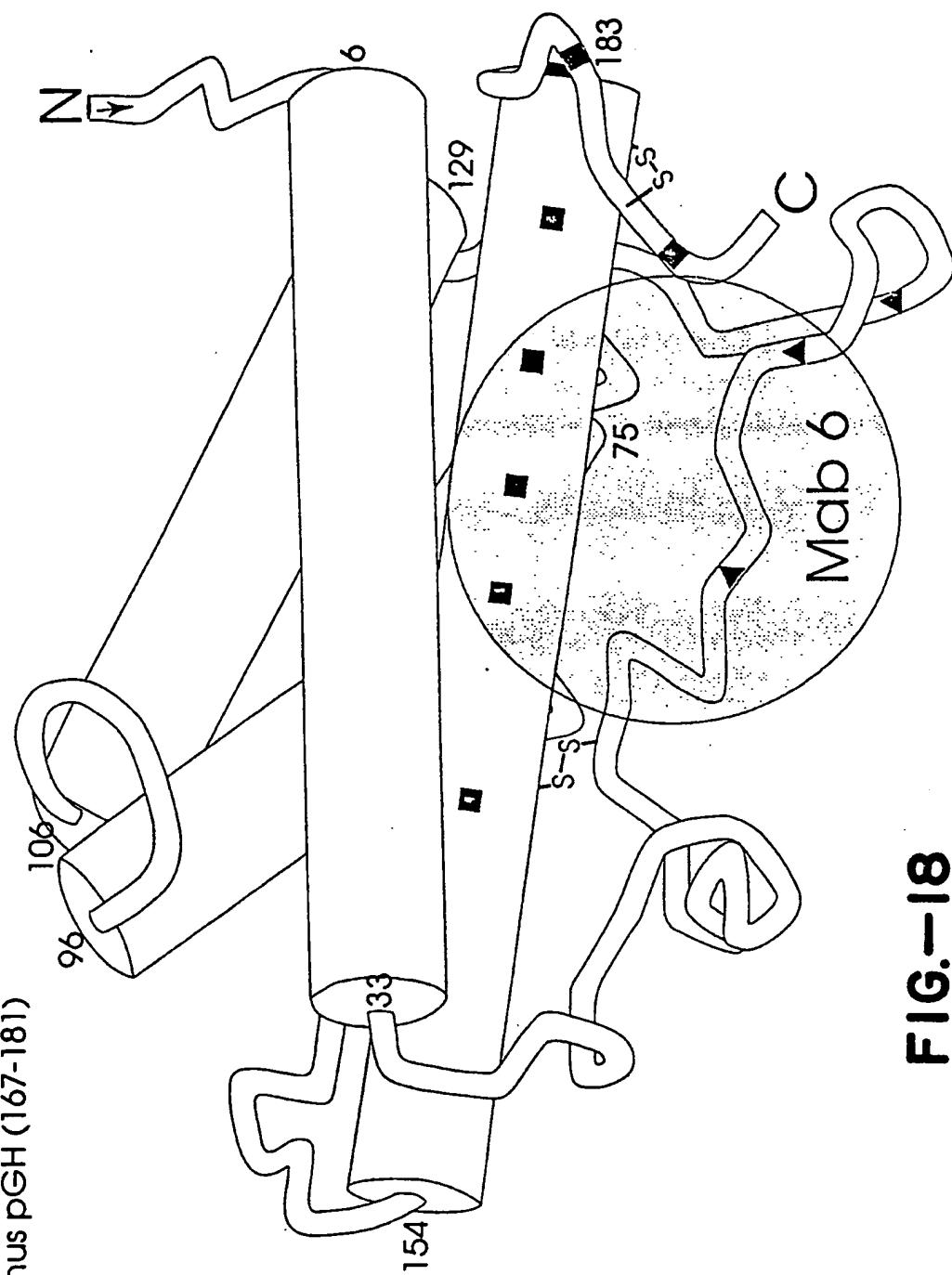
▲ pGH (57-73) minus hPRL (54-74)
 ■ pGH (164-190) minus pGH (167-181)
 ● C182A

▲ ■ ●

FIG. — 17

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▲ pGH (57-73) minus hPRL (54-74)
 ■ pGH (164-190) minus pGH (167-181)

FIG.-18

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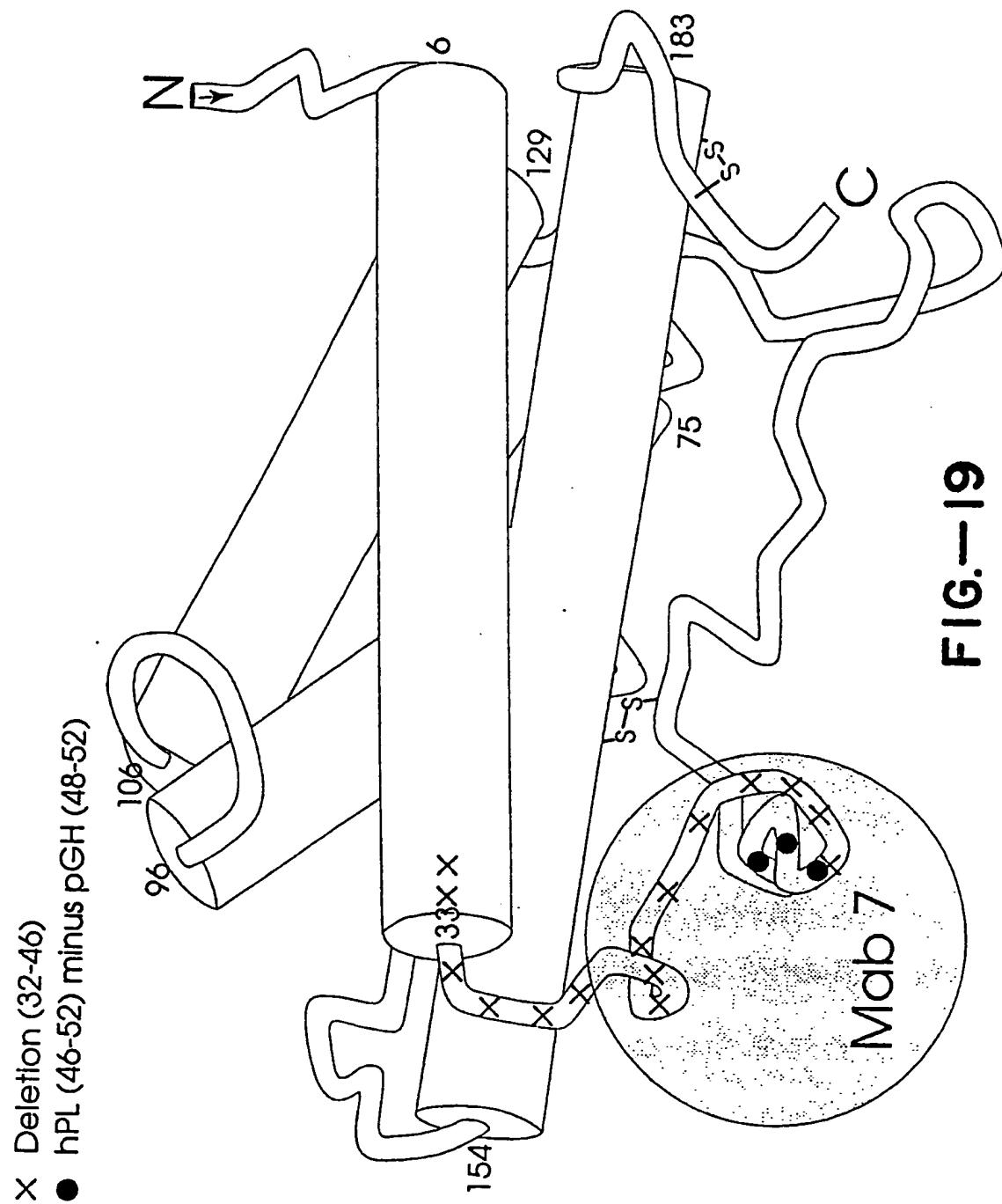


FIG.—19

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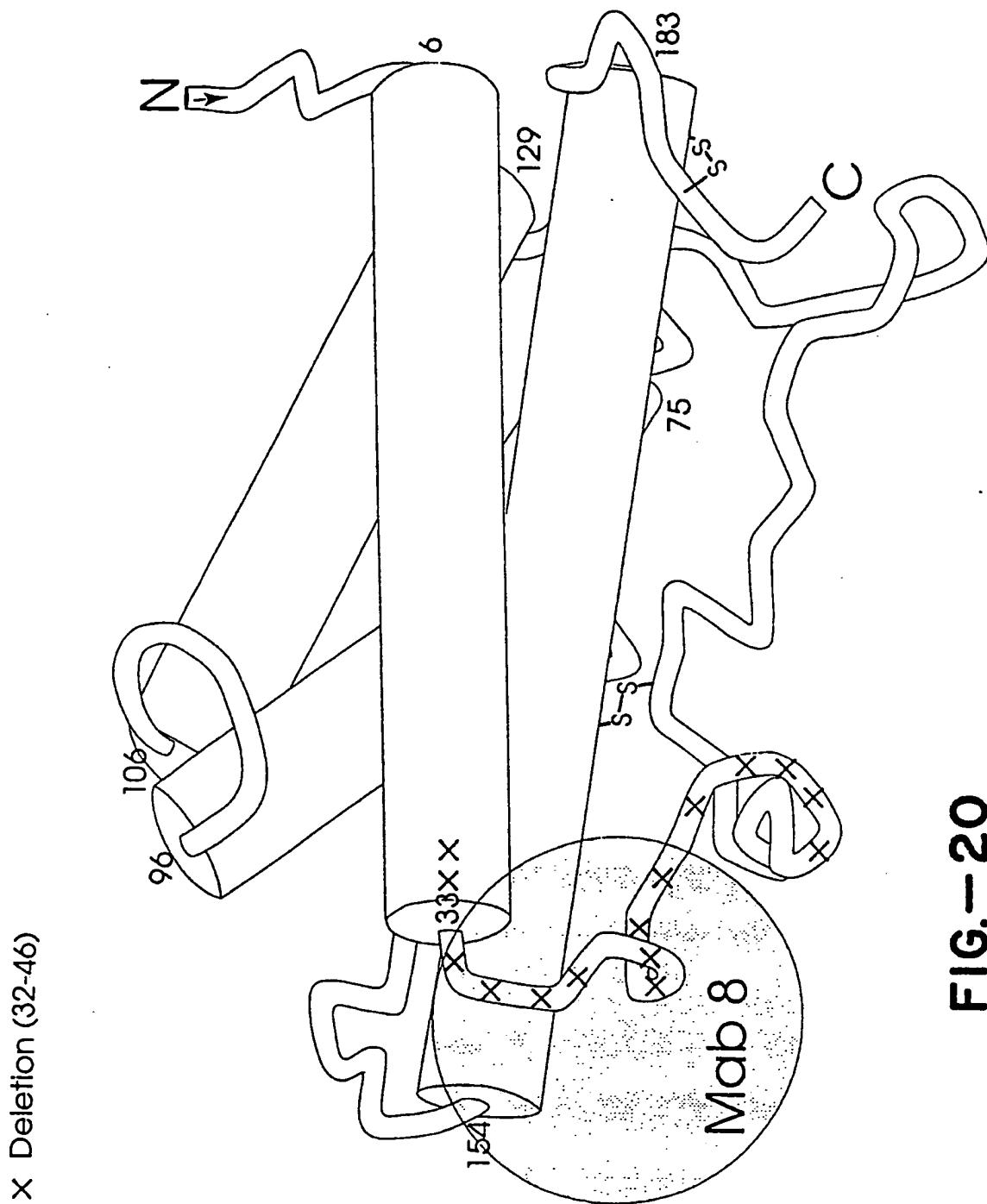
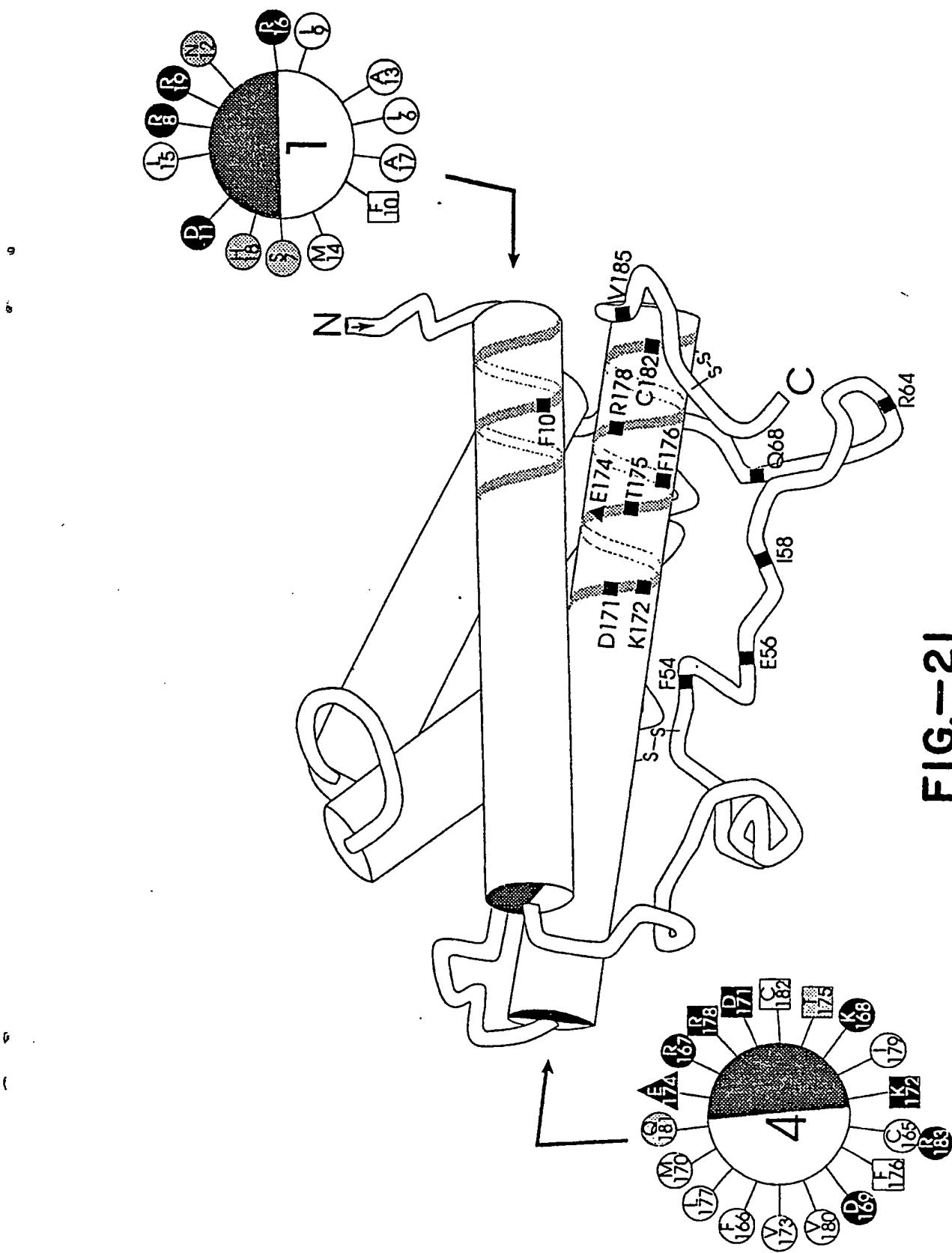


FIG.-20

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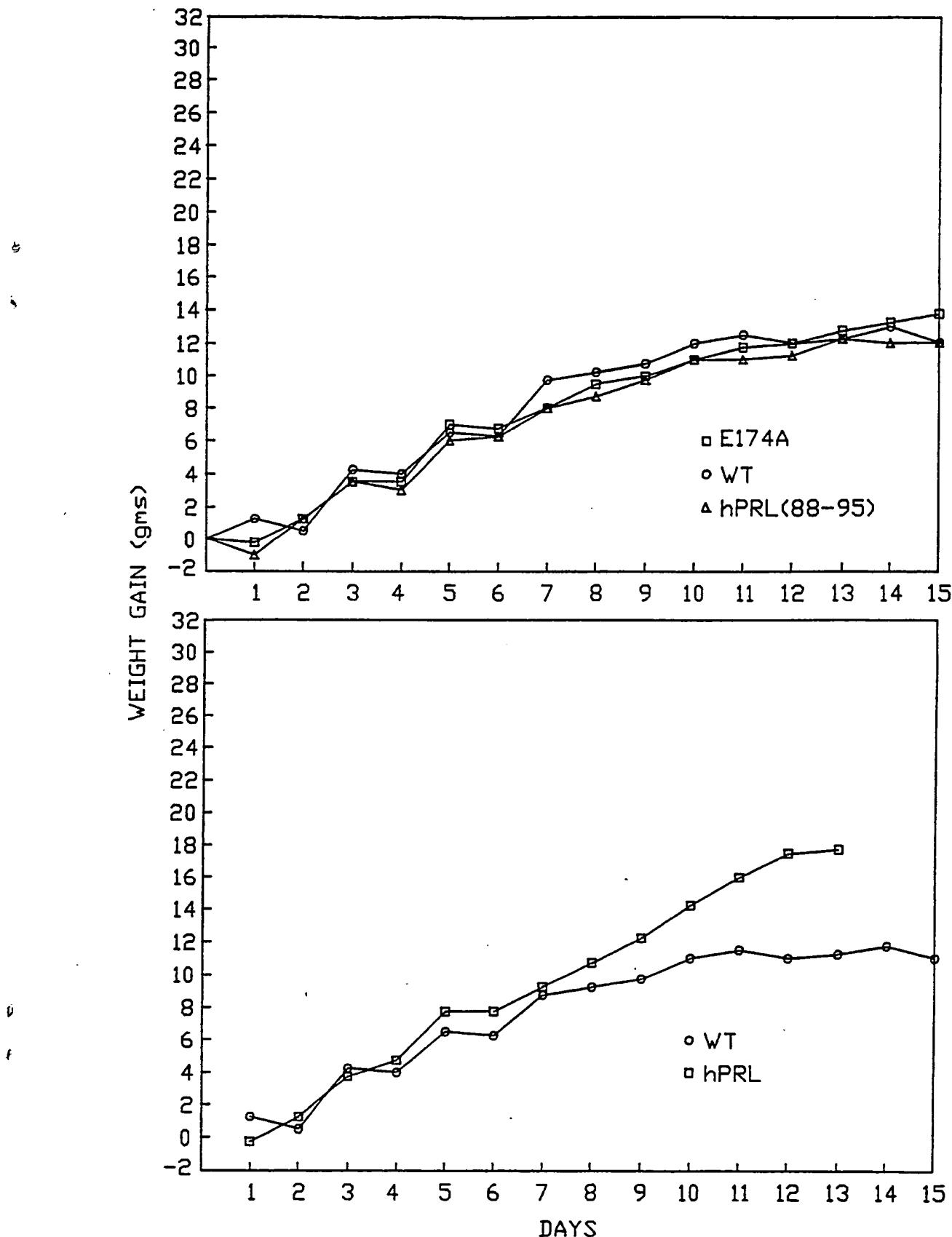


FIG.- 22

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GH ANALOG BIOPOTENCY IN RATS AFTER 8 DAYS OF TREATMENT

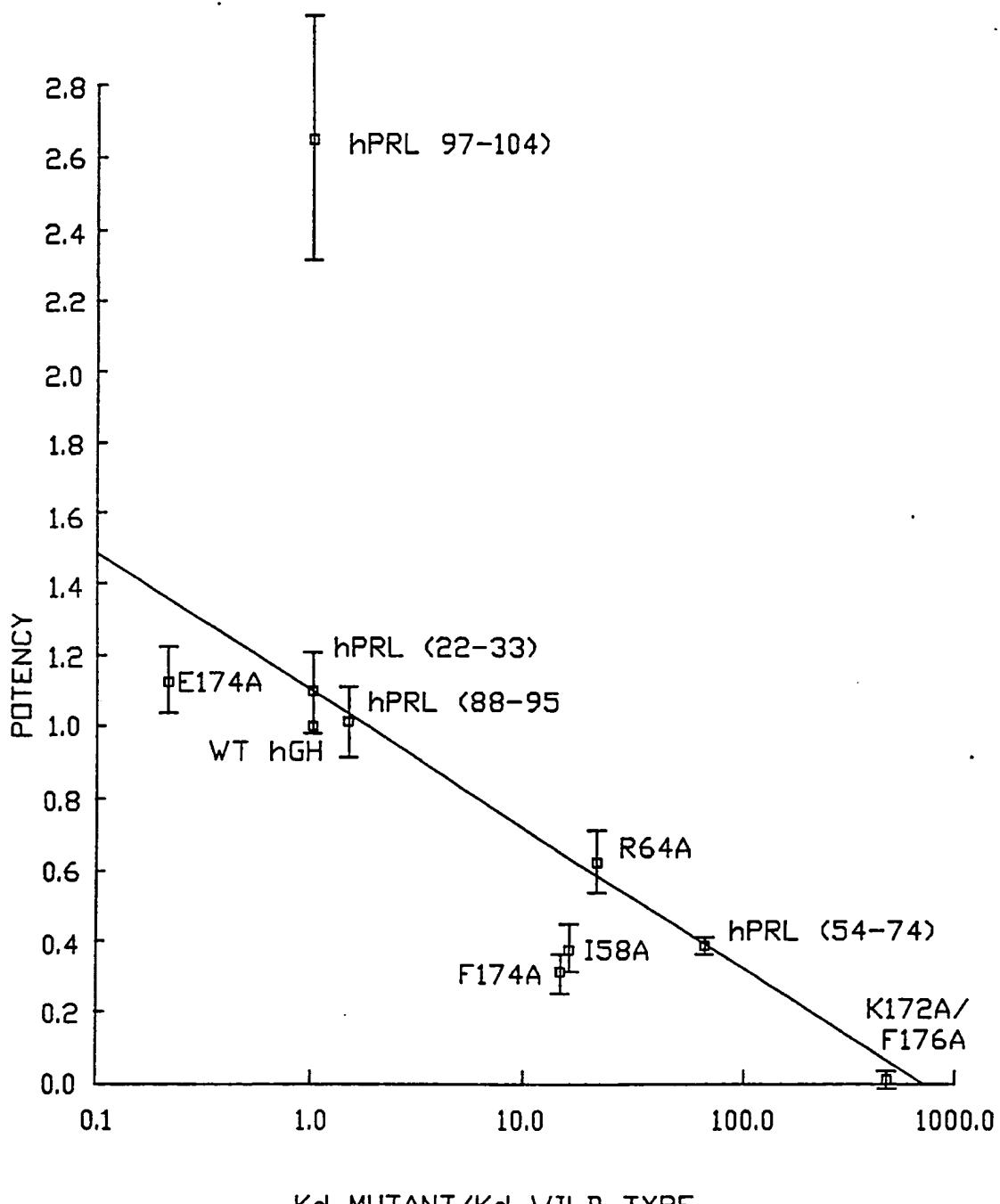


FIG.-23

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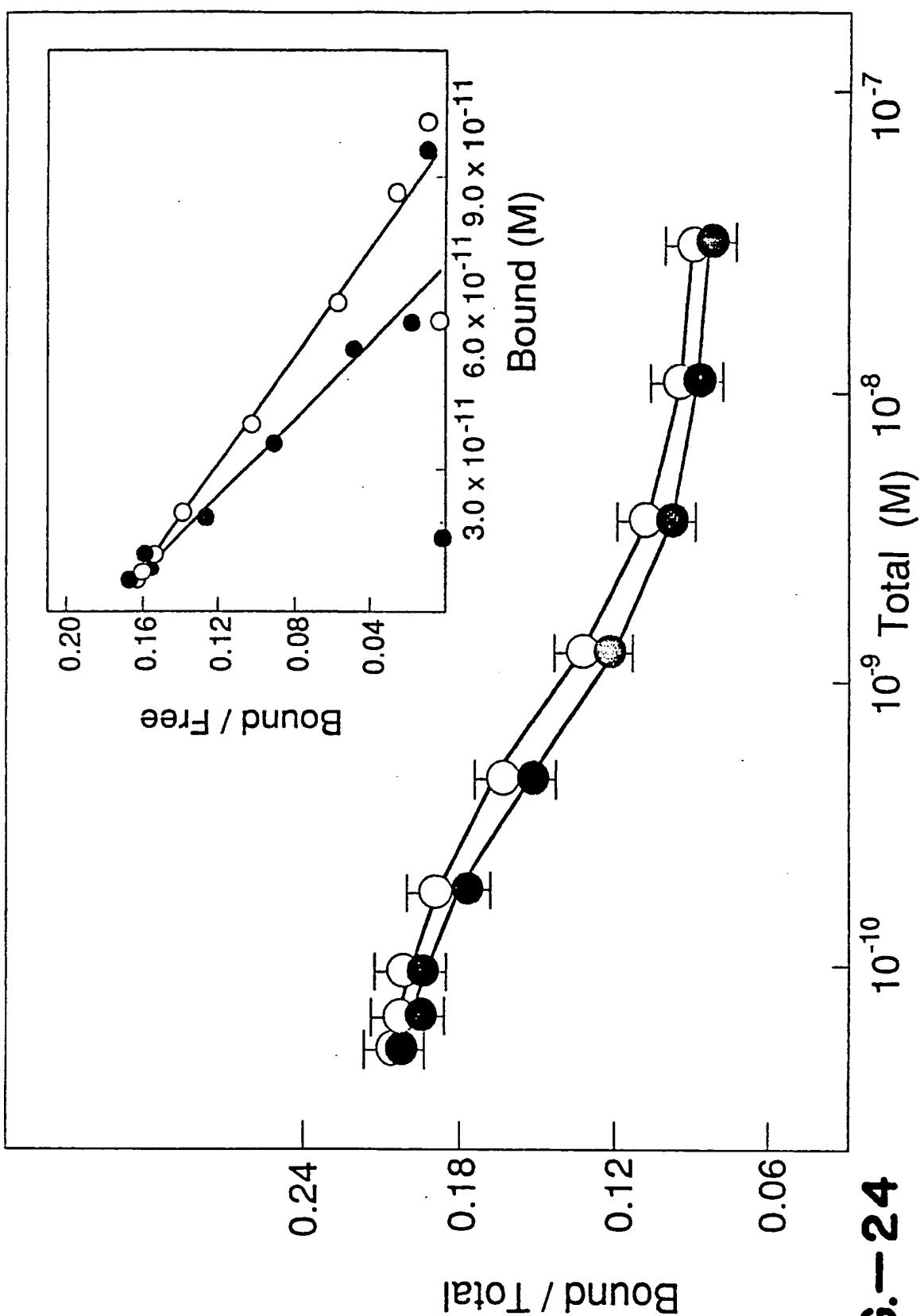


FIG.-24

Binding Determinants for hGHR

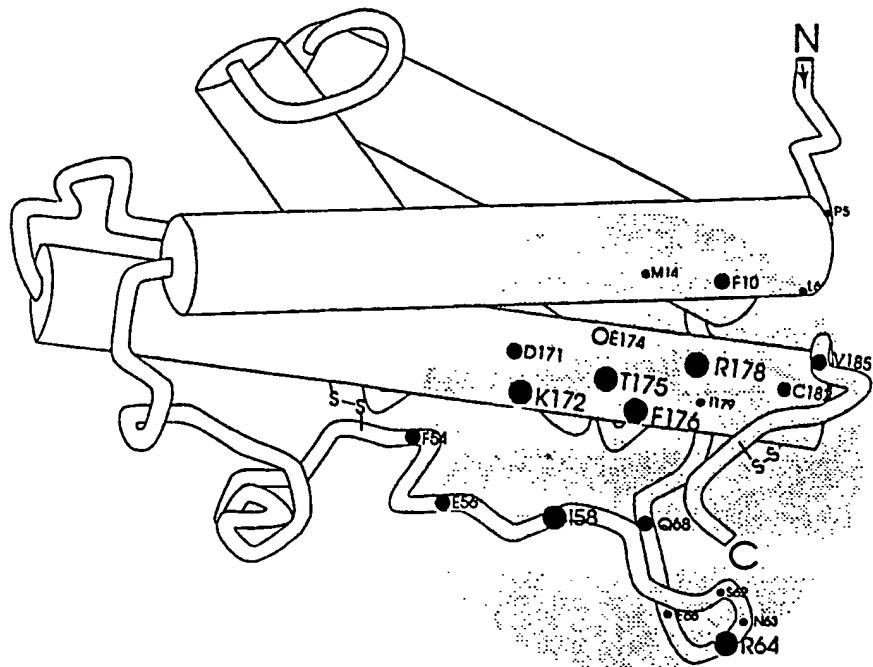


FIG.- 25A

Binding Determinants for hPRLr

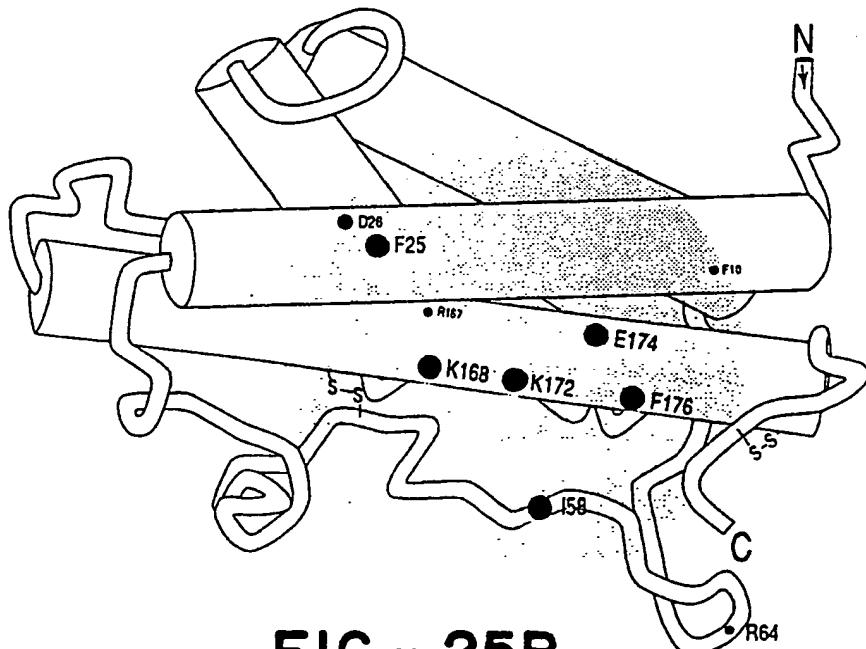


FIG.- 25B

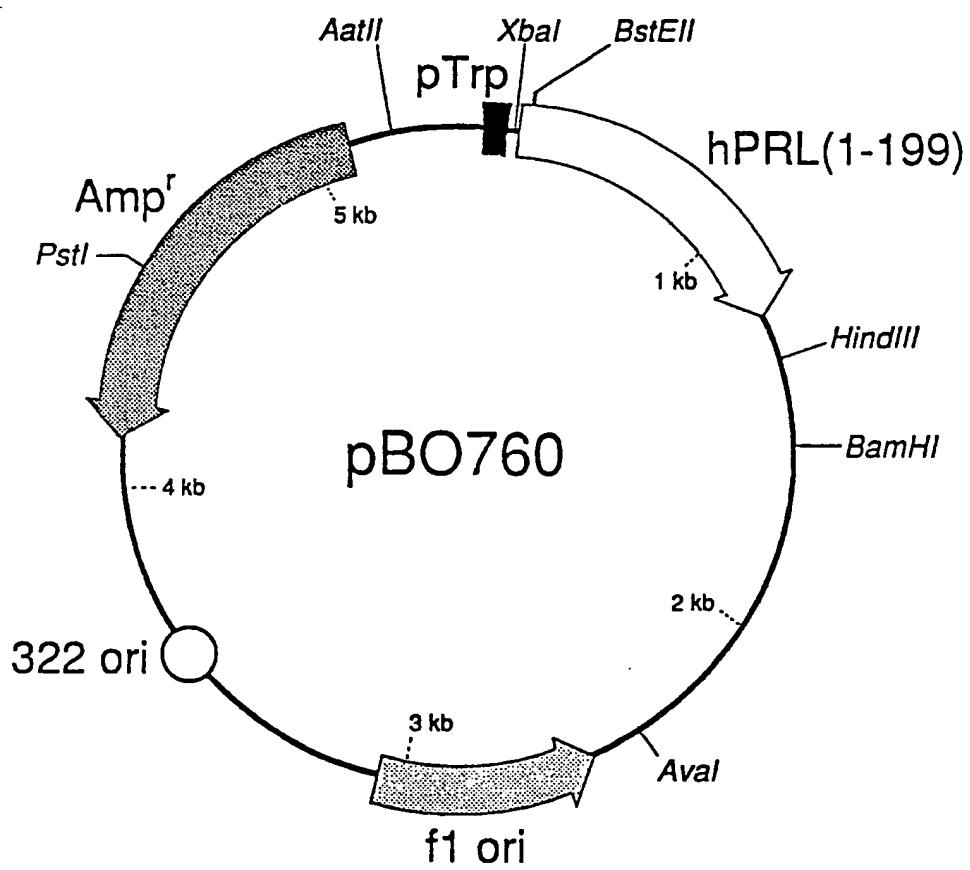


FIG.-26

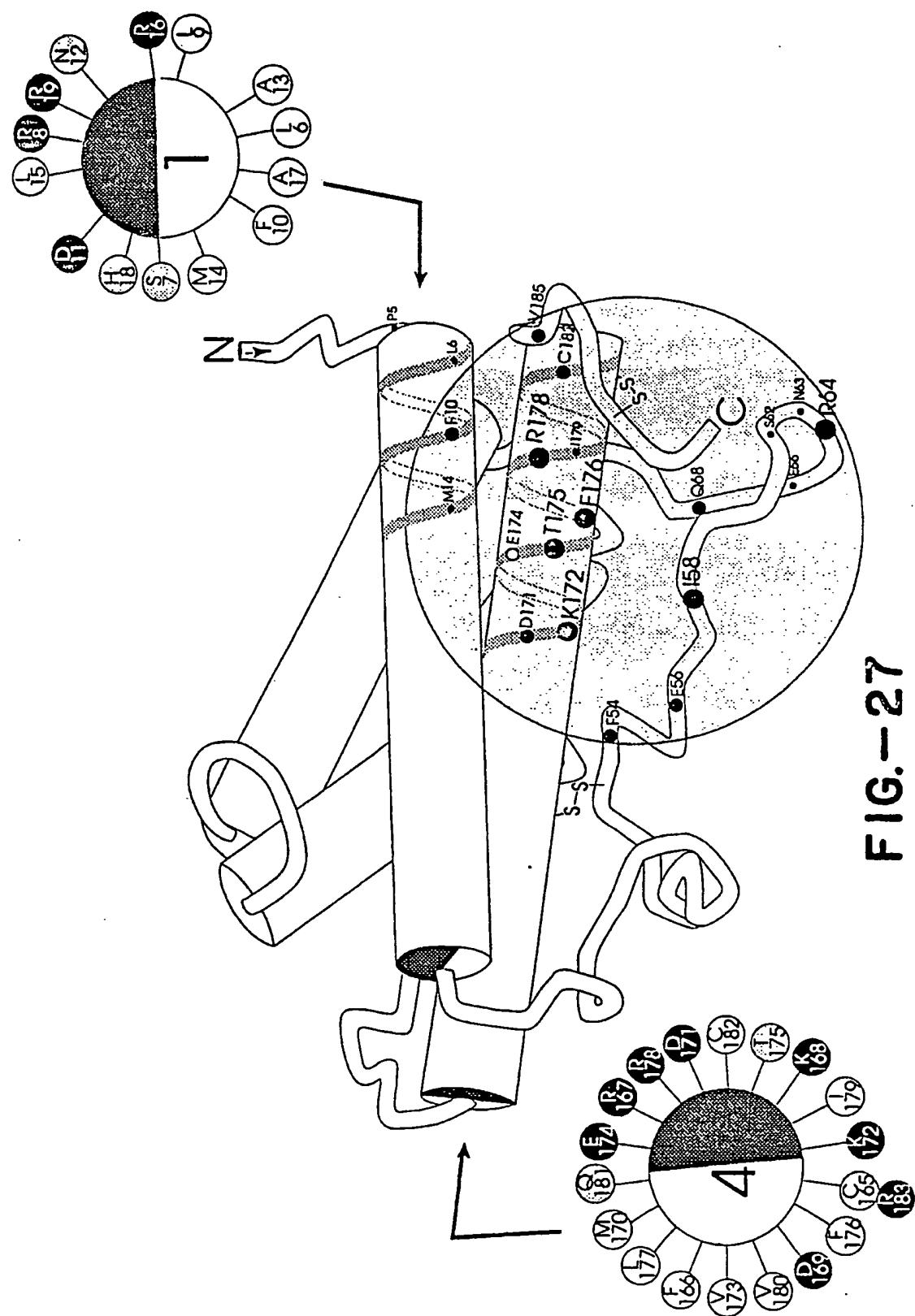
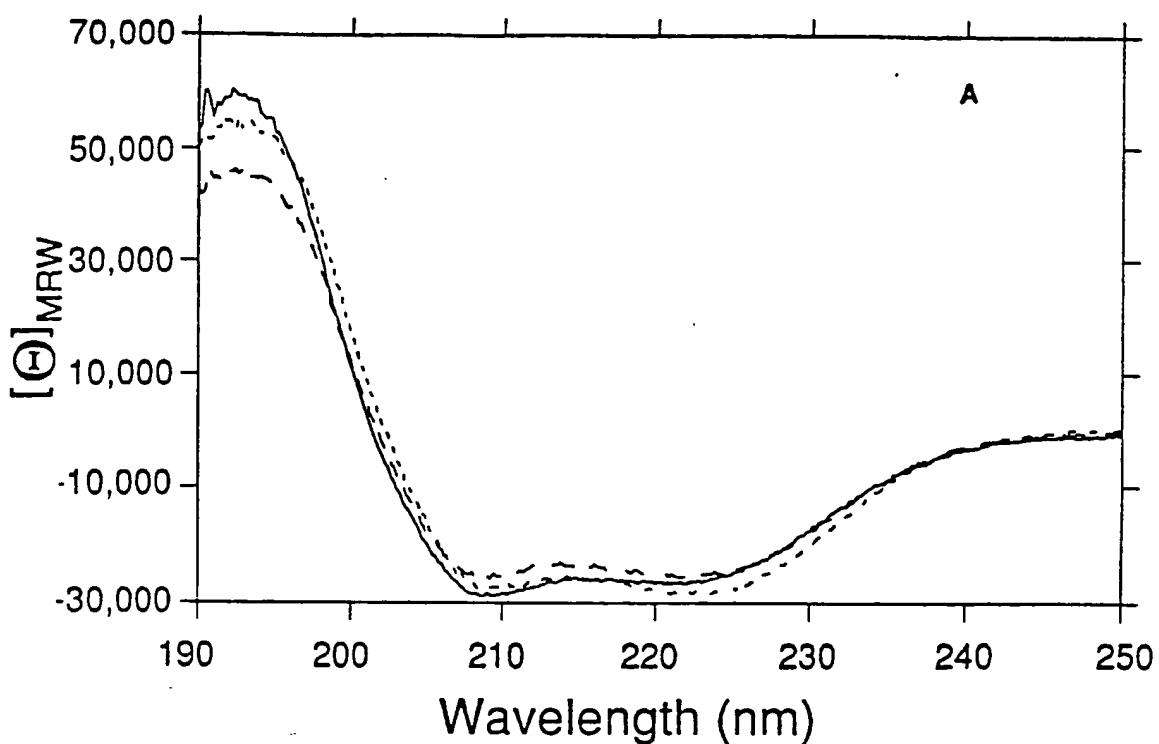
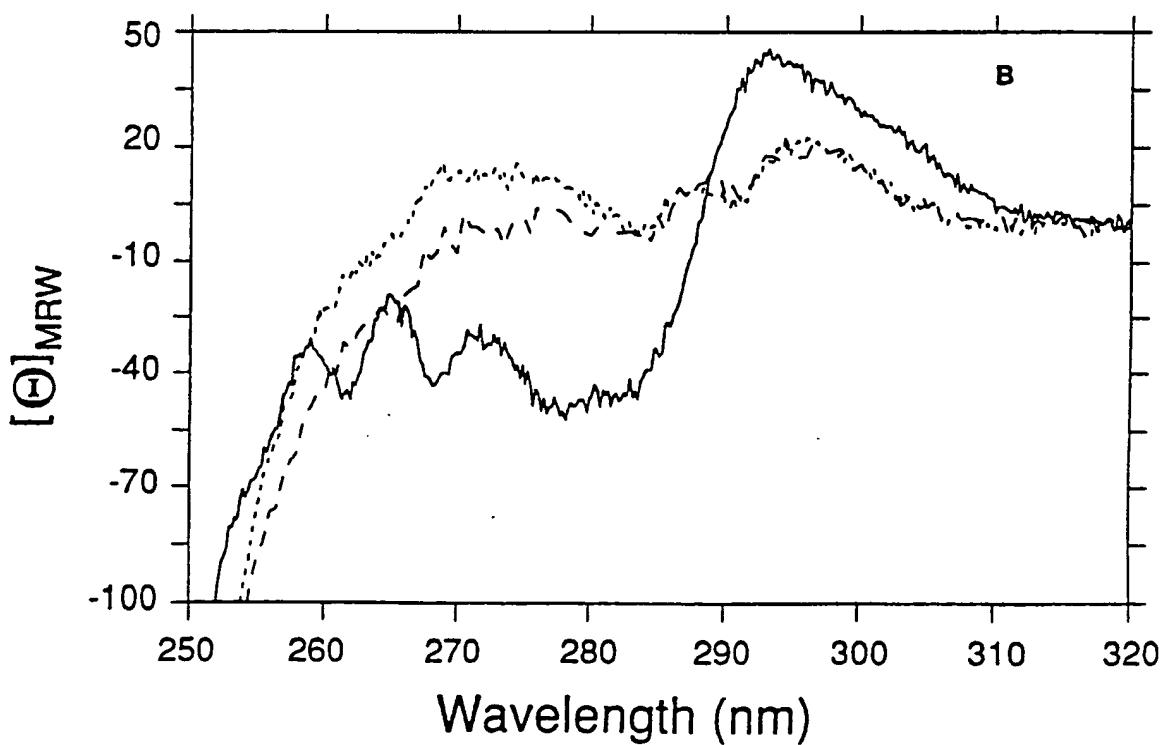


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**FIG.-28A****FIG.-28B**

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FIG. - 29

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04778

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): G01N 33/53, 31/00, 33/543, 33/567, 33/566

U.S. Cl: 435/7; 436/501, 504, 518, 548

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
U.S.	435/7; 436/501, 504, 518, 548; 935/79, 81

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *CHEMICAL ABSTRACTS SERVICE ONLINE, BIOSIS PREVIEWS,
AUTOMATED PATENT SYSTEM

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X,P	Science, Volume 244, issued 1989, CUNNINGHAM, B.C., ET AL, "High Resolution Epitope Mapping of hGH-Receptor Interactions by Alanine-Scanning Mutagenesis", 1081-1085.	1-13,16-31
X,P	Science, Volume 243, issued 1989, CUNNINGHAM, B.C., ET AL, "Receptor and Antibody Epitopes in Human Growth Hormone Identified by Homolog-Scanning Mutagenesis", 1330-1336.	1-13,16-31
A	Biochem. Biophys. Res. Commun., Volume 135, issued 1986, SOUROUTON, M.C., ET AL, "Localization of a Highly Immunogenic Region on the Acetylcholine Receptor Alpha-Subunit", 82-89.	1-13,16-31

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

02 February 1990

Date of Mailing of this International Search Report

05 MAR 1990

International Searching Authority

ISA/US

Signature of Authorized Officer

Karen Krupen
KAREN I. KRUPEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Endocrinol., Volume 121, issued 1987, WERTHER ET AL, "Localization and Characterization of Insulin Receptors in Rat Brain and Pituitary Gland Using In-Vitro Autoradiography and Computerized Densitometry, 1562-1570.	1-13,16-31
A	Endocrinology, Volume 107, issued 1980 MILLS, T.B. ET AL, "Fragments of human growth hormone produced by digestion with thrombin: chemistry and biological properties", 391-399 (See Abstract, 143544)	1-13,16-31
A	Chemical Abstracts, Volume 108, no. 11, issued 1988, (Columbus, Ohio, U.S.A) B. C. Cunningham, "Improvement in the alkaline stability of subtilisin using an efficient random mutagenesis and screening procedure", Abstract.	1-13,16-31

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹**

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers because they relate to subject matter¹² not required to be searched by this Authority, namely:

2. Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

3. Claim numbers....., because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

(See Attachment).

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers: 1-13 and 16-31

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

The additional search fees were accompanied by applicant's protest.

No protest accompanied the payment of additional search fees.

Part IV. Before #1, Observations

I. Claims 1-13 and 16-31 are drawn to a method for identifying unknown active domains in the amino acid sequence of polypeptides classified in class 436, subclass 501.

II. Claims 14, 15 and 32-64 are drawn to a method of forming a growth hormone variant and the growth hormone variants produced classified in class 530, subclass 350.

III. Claims 65-79 are drawn to human prolactin hormone variants classified in class 530, subclass 399.

IV. Claims 80-83 are drawn to human placental lactogen variants classified in class 530, subclass 399.

V. Claims 84-86 are drawn to DNA sequences and expression vectors and hosts classified in class 536, subclass 27.